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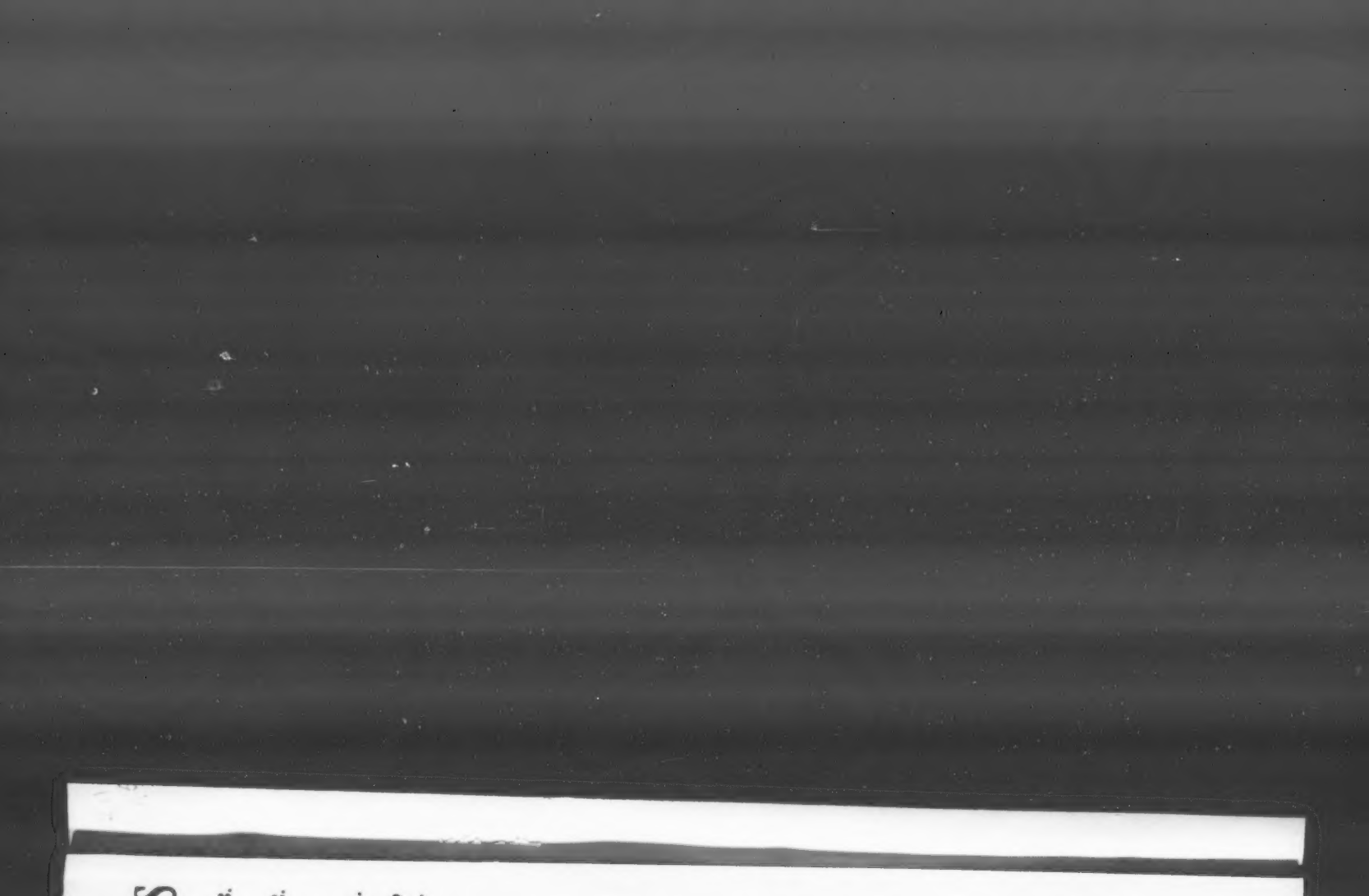

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JULY, 1914

ORIGINAL ARTICLES

CLINICAL OBSERVATIONS ON NINETY CASES OF ACUTE EPIDEMIC POLIOMYELITIS

By Francis R. Fraser, M.B.,

of New York.

(From the Hospital of the Rockefeller Institute for Medical Research, New York.)

In June, 1912, Peabody, Draper, and Dochez[1] published a report on 71 cases of acute epidemic poliomyelitis admitted to the Hospital of the Rockefeller Institute for Medical Research during the summer of 1911. During the summer and autumn months of 1912 and 1913, 90 cases were admitted to the Hospital, 57 in 1912, and 33 in 1913. The present paper reports the clinical observations made on the 90 cases admitted in 1912 and 1913, that seem to have importance from the fact that attention has not been drawn to them in earlier clinical accounts.

Cases were admitted during the acute stages only, and, after having remained in the hospital for from a few days to three months, they have reported at intervals since for observation and advice as to treatment. A far larger number were seen in the dispensary and were not admitted, as the acute stages were passed. In addition to the 90 cases admitted during 1912 and 1913, 7 cases were admitted on the possibility of their condition being due to acute poliomyelitis. The steady decrease in the number of admissions was due to a decrease in the number of cases of the disease in New York, and in addition to the decrease in numbers, a decrease in severity was observed, for in the 71 cases admitted

[1] A Clinical Study of Acute Poliomyelitis. Monograph No. 4, June, 1912. The Rockefeller Institute for Medical Research.

during 1911, Peabody, Draper, and Dochez reported a mortality of 14 per cent., while among the 57 cases admitted during 1912, the mortality was 16 per cent., and among the 33 admitted during 1913 it was 9 per cent. Furthermore, the 3 fatal cases of 1913 died of secondary inflammatory conditions of the lungs, and not directly from the disease. The resulting paralyses, however, were as widespread and complete in 1913 as in the previous years.

ETIOLOGY. The ages of the patients varied from nine months to fourteen years. In three instances two members of a family were admitted, and in a fourth instance two cousins living in the same house. It was further observed that although only in a very few instances could a direct or indirect contact with a patient suffering from the disease be recorded, at any one time the majority of patients came from the same general locality in New York. Inquiries were made as to the prevalence of flies and other insects in the house, and subsequent to the communication of Rosenau[2] on the conveyance of infection by the stable fly (Stomoxys calcitrans), the proximity of the home to stables was in all cases inquired into. Neither the prevalence of insects nor the neighborhood of stables was found to be a usual occurrence. In many cases the parents suggested some slight accident or some dietary indiscretion as the cause of the condition, but in no case could a predisposing cause be ascertained.

In view of the possible importance of the nose and throat as the point of entrance of the infection, the tonsils were in all cases inspected.[3] Simple inspection is unsatisfactory in estimating the size or condition of tonsils, but in 37 cases they were noted as somewhat enlarged and congested, in 18 cases as enlarged, and in 4 as slightly congested. In the remaining 31 they were noted as normal or were not examined, as occurred in two rapidly fatal cases. In the case of 8 children whose tonsils were noted as enlarged and congested, 21 other children in their families were examined, and of these in 16 the tonsils were noted as showing no enlargement or congestion. In 15 cases the tonsils were enucleated, and on removal usually proved to be larger than inspection had led one to expect.

SYMPTOMATOLOGY. 1. *Preparalytic and General.* While no cases were admitted in the preparalytic stages, 5 abortive cases were admitted, and in 22 cases the paralysis increased after admission to the hospital. The preparalytic and general symptoms were in all cases inquired into, and are important in view of early diagnosis. These symptoms were observed by the parents or attendants for from a few hours to nine days before the onset of paralysis, but all of them were further observed in the cases after

[2] International Congress of Hygiene and Demography, Washington, 1912.

[3] Leiner and Weisner, Wien. klin. Woch., 1910, xxiii, p. 323; Flexner, S., The Contribution of Experimental to Human Poliomyelitis, Jour, Amer. Med. Assoc., 1910, lv, pp. 1105-1113.

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admission to the hospital and might continue until the acute general symptoms passed off. The most common symptom was *feverishness*, and this was reported to be present in 79 of the cases. It was not constant, but might appear for a day or two and then disappear before the onset of paralysis, or it might appear only after the onset of paralysis. In the records of the temperature (rectal) after admission a high temperature was exceptional, and while one case was admitted with a temperature of 104.8°, and in the fatal cases temperatures of 104° to 105° were observed before death, a temperature that varied from 101° to 103° and gradually settled in the course of a few days was seen in the majority of cases. The temperature may be settling some days before the cessation or spread of paralysis, but it was usually still slightly elevated for some days after further spread of the paralyses was observed. A child, aged three years, was readmitted for observation four months after the onset, and at that time an afternoon temperature of 100° or over was of daily occurrence, although there was no evidence of a recurrence or of any other cause of an elevation of temperature. The pulse rate did not, as a rule, settle until some days after the temperature was normal, and in a few cases showed the irregularities of sinus arrhythmia. The pulse rate was commonly between 120 and 140 on the day of admission. *Drowsiness or heaviness* was noted in 47 cases, and this was very variable in degree, for sometimes an apparently comatose condition was present, from which, however, the child could be readily aroused. Accompanying this heaviness there was a condition of *irritability or restlessness*, best seen when the child was aroused, and frequently connected in the older children with fear of pain consequent on handling. The restlessness was also observable during sleep, the child tossing about and rolling the head from side to side. In spite of the drowsiness the children seldom slept well, being wakeful and querulous, and this was in marked contrast to the sound, uninterrupted sleep seen in early convalescence. During sleep, definite involuntary *twitchings or jerkings* were seen in 20 of the patients. These jerkings were seen as short, sudden movements either of flexion or extension of a limb, and frequently in a limb that subsequently became paralyzed. The movement might involve upper and lower limbs on one side of the body, both lower or both upper limbs, or all four limbs, or head and neck, or the whole body at once. A totally paralyzed part never showed such movement, but it was most frequent in a limb that showed a slight weakness. It was not observed after the acute general symptoms passed off. A fine tremor was seen in a few of the patients similar to that described by Netter and others.[4] A lateral nystagmus was seen in one patient, and though not

[4] Paralysie infantile choreique, Arch. de Méd des Enfants, December, 1913.

constant, it was present without any voluntary movement of the eyeballs. A history of a localized, profuse *sweating* was occasionally obtained, involving the part that subsequently became paralyzed, but more common was profuse general perspiration in the very severe cases. This general perspiration occurred both when the child was awake and when it was asleep, but was usually more profuse during sleep. It did not cease with the other acute symptoms or with the fall of temperature, and in one case was still well marked, though diminished, at the end of six months.

Gastro-intestinal symptoms were rarely absent, and vomiting was reported in 41 cases and loss of appetite in 22 others. Diarrhea,[5] which has been reported as common in some epidemics, was rarely given as a symptom, and was noted in only 7 cases, while constipation was a marked feature in 38 of the patients. After admission the patients in the acute stages were very thirsty, but had no appetite for solid food. When the acute symptoms disappeared, the appetite returned at once and was usually vigorous. Convulsions occurred only once, and rigors were never noted.

A symptom of considerable importance, in that it is observed early and that it is not present in gastro-intestinal disturbances, nor, as a rule, in the common infectious diseases, is the *stiffness of neck and back*, resistance to anterior flexion of the neck and back, or pain on attempting such flexion. This was present in 72 of the cases, and persisted for from one day after admission to three or more weeks. Of the 18 children who did not show this resistance, in 7 the posterior muscles of the neck and back were paralyzed, and the others were mild cases or were seen for the first time late in the disease. In three instances there was definite head retraction, with arching of the back, and in several more the patient was restless unless placed in a position that would allow of slight arching or retraction. This symptom was present to a marked extent in cases with only slight paralysis, and was the most marked feature in two cases classed as abortive. On the other hand, cases with extensive or severe paralysis showed slight stiffness and resistance to anterior flexion, and there was no relation between the degree of abnormality of the spinal fluid and the degree of resistance.

Pain and tenderness are important symptoms of the acute stage, and are sometimes observed before any paralysis is noted. Tenderness on handling was noted in 61 of the cases, and many more showed signs of pain when neck and back were flexed. In many cases the tenderness on handling was due to flexion of the neck and back, but in others it had no connection with such movement. It might be generalized and cause the child to dread the approach of anyone likely to handle him. In other cases it was localized

[5] Krause, P., Deut. med. Woch., 1909, xxxv, 182.

to a limb or limbs, usually the parts paralyzed. This tenderness during the acute stages seemed to be of three types or degrees. In a few cases a hyperesthetic condition of the skin was suspected, but in dealing with patients of the age and condition under observation, accurate determination of such a point is difficult. In a few others, mild pressure on the muscle masses caused pain, not specially localized over the nerve trunks. In many more, passive movements that would stretch tendons or capsular structures caused the child to cry out with pain. This tenderness was seen frequently in limbs, that at no time showed paralysis, but the deep reflexes were usually absent. On the other hand, it could be elicited in limbs that were totally paralyzed. It frequently caused a child to keep a limb that was not paralyzed at rest and simulate paralysis, the true condition of the limb being ascertained only by handling. This tenderness, as a rule, passed off in a day or two, but might persist for three or four weeks. It constantly persisted after further spread of paralysis was noted, and passive movements increased rather than decreased its severity. After the acute stage was passed a different type of pain on passive movement was observed. If a limb were allowed to remain at rest after the acute stage, the capsular structures, tendons, and muscles appeared to stiffen, and in these cases the tenderness decreased with treatment by passive movements. This tenderness was usually localized more to the region of joints, and occurred in joints the muscles controlling which were completely flaccid as well as at joints where the muscles were only partially affected, and simulated the joint pain of an arthritis, but without local points of tenderness on pressure. Yet another type of tenderness must be noted. Some weeks after the onset a limb that has hitherto shown no sign of paralysis becomes painful on movement, the child does not use it freely, and the part appears to be paralyzed. This was well seen in a child whose left upper limb alone was paralyzed. Three weeks later, when the child was allowed to run about, she complained of pain in the knees and seemed unable to walk. On admission it was found that the muscles of both lower limbs were spastic and that the tendon reflexes were all exaggerated. The pain was situated in the flexor tendons at the back of the knees. Massage and movements relieved the stiffness, and the pain disappeared. It is possible that in such cases irritation to the pyramidal tracts results during the healing process of the lesion in the upper part of the cord.

Spontaneous pain is difficult to ascertain in patients of the age usually affected, and frequently what appeared at first to be spontaneous pain would disappear on adjusting the position of the patient to avoid tension on muscles or ligaments. In one case the pain could not be relieved by adjustment of position and seemed to be independent of such adjustments. This pain disappeared

with the other acute symptoms. In this case, a girl, aged four years, there was present for two days after admission an apparent absence of sensibility to painful stimuli, as pricking with a pin caused no response, but the child was in a comatose condition at the time, and the sensibility returned as the coma passed off and the spontaneous pain manifested itself.

2. *Paralysis.* Wickman[6] has differentiated eight types of the disease, based on the fully developed symptomatology. The distinction between these types depends on the localization of the lesions in the central nervous system. Any part of the brain and cord may be affected, and in any one case the lesions may be widespread, or lesions may be present giving at one time a paralysis of the muscles of the face and of a lower limb. The different types cannot then be rigidly differentiated, and the distinction between the meningeal and the abortive types is often extremely difficult. Müller[7] classifies all cases that do not show definite paralysis as abortive, and it is simpler to adopt his classification in this respect. Of the paralyzed cases, the differentiation of bulbospinal and cerebral types has been suggested, and though rarely cases of definite spastic paralysis are found, it is more common to find spastic and flaccid conditions coexisting.

Involvement of the *respiratory* musculature is of importance in its prognostic significance; 11 of the 12 fatal cases may be included in this group. In 7 of them death was due directly to the respiratory embarrassment, and in the remaining four it was due to secondary inflammatory conditions in the lungs. In 1 other fatal case death was due to an inflammatory condition of the lungs secondary to a paralysis of the muscles of the palate and pharynx. Of the 31 cases showing involvement of the muscles of respiration, there was paralysis or weakness of both diaphragm and intercostals in 9, and of these, 6 ended fatally while in the hospital. In 3 cases the diaphragm alone was involved without complete paralysis, and in each instance there has been complete recovery in the action of the diaphragm; 19 cases showed paralysis, complete or partial, of the intercostal muscles, and of these, 3 ended fatally and 7 recovered entirely. In no instance was the respiratory paralysis the only paretic symptom. The prognosis as to life is always grave when the respiratory musculature is weakened, and though severe paralysis of the kind is readily observed, a weakness of either diaphragm or intercostals is easily overlooked and may be the commencement of a spread that will terminate fatally. Rapidity of respiration is not necessarily present with slight weakness or limited paralysis, as either the diaphragm alone or the intercostals alone are able to carry on efficiently the movements of respiration, and even when

[6] Beiträge zur Kenntniss der Heine-Medinschen Krankheit, Berlin, 1907.
[7] Die Spinale Kinderlähmung, Berlin, 1910.

present, the rapid, shallow respirations may be erroneously considered part of the general acute condition. If the chest is prevented from expanding by pressure on the thoracic wall, a weakened or asymmetrical action of the diaphragm can be estimated by observing or palpating its movements in descending and ascending in the abdomen, while pressure on the abdomen to limit or prevent the descent of the diaphragm will demonstrate the power of the intercostals to carry on respiration by expanding the thorax. As with any part of the body musculature, weakness of the diaphragm and intercostals may appear and disappear again in the course of a few hours.

The large number of cases showing involvement of *facial* muscles was striking. Of the 90 cases, 31 showed weakness of the muscles of the face, and in many more a slight involvement was suspected. In 5 cases this was the only paretic symptom, while in the remaining 26 other parts of the body were involved. In 1 case, which showed many unusual factors and which will be discussed more fully later, the weakness of the facial muscles was bilateral. In 7 cases the whole of the muscles of one side of the face were paralyzed. The others, while showing a definite asymmetry, showed a weakness of the whole of one side or a paralysis or weakness of the upper or lower parts of the facial musculature only. Of the 5 uncomplicated cases, 3 showed a definite exaggeration of the tendon jerks in the upper and lower limbs, in a fourth the tendon reflexes seemed normal, and in the fifth the tendon reflexes of the upper limbs were diminished, while those of the lower limbs seemed normal. Among the cases complicated by paralysis of other parts of the body, spasticity and exaggerated reflexes were occasionally met with, but not to a greater extent than among cases showing no involvement of cranial nuclei. In the case of a girl, aged three years, admitted on the fourth day after the onset of symptoms and the third day after the appearance of paralysis, and showing involvement of the left side of the face, of the laryngeal and pharyngeal muscles, and to a slight extent of the respiratory musculature, all the tendon reflexes were exaggerated on admission. Without any paralysis of the extremities developing, the tendon reflexes gradually diminished and were lost in the course of the next two days until the only one obtainable was the right Achilles reflex, and it was but a feeble response. In 3 cases the facial weakness cleared up in the course of a few weeks, and in 5 of them no sign of facial involvement was apparent after an interval of from three to six months. At the end of that time 3 had shown no improvement, while 16 showed distinct improvement, and the remaining 4 died during the acute stage of respiratory involvement. One case deserves special notice in that an almost complete ptosis of the right upper eyelid was the only paretic symptom on admission, though when seen again six months later, slight weakness of the

lower part of the face on the right side and of the right external rectus could be demonstrated, while the ptosis had almost entirely disappeared.

Difficulty with *micturition* is fairly common, and is probably due to a local rather than to a general weakness, for it occurs in cases that show slight paralysis of the limbs as well as in severely paralyzed cases and in cases that show few general symptoms. The difficulty of *defecation* is usually associated with the paralyzed or weakened muscles of the abdominal wall, but in one case the anal sphincter was observed in a patulous condition for a few days.

3. *Abortive Cases.* Five of the cases were considered to be examples of the abortive type. In 3 no history of direct or indirect contact was obtainable, and the illness commenced with fever, vomiting, or loss of appetite and constipation, with in 2 cases general weakness and twitchings of the limbs and pains in the knees. On admission all three showed marked stiffness of the neck and back, and their spinal fluids contained 101, 34, and 9 cells respectively per cubic millimeter. The fluid with 9 cells per cubic millimeter contained a marked excess of globulin, and in all the mononuclear cells predominated. No paralyses were discoverable, though some of the tendon reflexes were exaggerated and others diminished, and nothing suggestive of any of the common acute infections in children was found. Two of them recovered entirely in the course of a few days, while the other was somewhat stiff and ataxic for four weeks. The fourth case was that of a boy, who lived in the same house with his cousin, admitted at the same time with paralysis. He was feverish and irritable at the commencement, and on admission, four days later, showed marked head retraction, but no characteristic changes in the spinal fluid. No paralyses were observed, and he had completely recovered three weeks later. The fifth case was the brother of a child admitted two days previously with paralysis, and he was admitted after a typical history of onset, with a temperature of 103.4°, no stiffness of the neck, but with 89 cells per cubic millimeter in his spinal fluid. In the course of two weeks his spinal fluid became normal, but he remained heavy and did not recover his appetite or his spirits. No tubercle bacilli were found in his spinal fluid, but he died three months later with a rapidly terminating tuberculous meningitis. It is possible that the original diagnosis of acute poliomyelitis was incorrect in this case.

Diagnosis. In the preparalytic stages and in abortive cases the diagnosis of acute poliomyelitis is always a matter of difficulty, and until some specific bacteriological or immunological test is devised, reliance must be placed on the general symptoms and on the character of the spinal fluid.[8] The occurrence at the time of an

[8] Peabody and Draper, A Study of Cerebrospinal Fluid and Blood in Acute Poliomyelitis, Amer. Jour. Dis. of Children, 1912, iii, p. 153. Fraser, F. R., A Study of the Cerebrospinal Fluid in Acute Poliomyelitis, Jour. Exper. Med., 1913, xviii, p. 242.

epidemic is strong evidence in a case where the diagnosis would otherwise be doubtful. The character of the spinal fluid in other acute infections is not at present sufficiently established for much reliance to be placed on the results of lumbar puncture in ruling out such infections. In its gross characters, in the cytology and in globulin content, the spinal fluid in tuberculous meningitis and in syphilitic myelitis closely resembles that seen in acute poliomyelitis, while the clinical features of these two diseases are often indistinguishable. This is well illustrated by two cases that follow:

CASE I.—L. B., a boy, aged two years and three months, had been a full-time child, difficult to bring up, but without any previous history of congenital syphilis. He was admitted with weakness of the right side of the face, right arm, and right leg, setting in after four days of drowsiness, fever, and gastro-intestinal disturbance. The paralysis was flaccid, there was no impairment of sensory functions, and there was definite stiffness of the neck. The child gave evidence of congenital syphilis in the bones of the skull, thorax, and limbs. The spinal fluid on admission contained 560 cells per cubic millimeter, mostly lymphocytes, and gave a heavy flocculent precipitate with the Noguchi test. The fever disappeared in a day or two, but the cells in the spinal fluid increased until a week after admission, when 1600 per cubic millimeter were present. The Wassermann reaction in the spinal fluid was positive, which is not found to be the case in acute poliomyelitis, and it was strongly positive in the serum also. He was transferred to the Babies' Hospital, and there the paralysis cleared up to a large extent after the intravenous administration of salvarsan.

CASE II.—W. L., a boy, aged twenty-two months, was reported to have been perfectly well until four days before admission, when he became feverish, vomited, was constipated, and his legs were paralyzed. On admission there was a flaccid paralysis of most of the muscles of the left leg. In the course of the next few days the paralysis spread to the right leg, to the face, to the external rectus of the right eye, and, to a slight extent, to both arms. On admission the spinal fluid contained 93 cells per cubic millimeter, and on the day of death, which occurred three weeks after the onset, it contained 451 per cubic millimeter, and tubercle bacilli were found in considerable numbers. No autopsy was obtainable, but before death the clinical picture was strongly suggestive of tuberculous meningitis. The cells were mostly lymphocytes, and the globulin reaction gave a definite precipitate, and, as in the previous case on admission, the clinical aspect and the findings in the spinal fluid were very simliar to those seen in acute poliomyelitis.

From the pathology of the disease it is possible that a lesion causing recognizable clinical signs may occur in any part of the brain and spinal cord. In 3 cases where unusual clinical signs

were present, a diagnosis of acute poliomyelitis was made. The cases occurred during an epidemic, and no other satisfactory diagnosis was supported.

CASE III.—A girl, aged nine years, was admitted after three days of slight feverishness, vomiting, and headache, with paralysis of the left side of the soft palate. The spinal fluid was normal, the child seemed quite well, and nothing else was discovered on physical examination. No diphtheria bacilli were found in the throat, and the condition of the palate cleared up in the course of two or three weeks. Serum from this patient protected a monkey from an intracerebral injection of poliomyelitis virus.

CASE IV.—The case of C. W. was diagnosed as polioencephalitis. The child was a boy, twenty-one months old, and the family history was satisfactory. He had had repeated gastro-intestinal disturbance, and had been rather troublesome to bring up. Ten days before admission he was very feverish and vomited. A day or two later there was some discharge from one ear. The fever continued, and he was drowsy and irritable. Four days before admission his left arm and leg seemed weak. On admission his temperature was 100°, pulse 80, respirations 24 per minute, and while the right arm and right leg were moved freely in all directions, the left arm and left leg were held rigid and were continually twitching. In addition, there was a rapid tremor of all limbs and of all the muscles of the body that varied in fineness and rapidity from time to time and was more marked in one part of the body than in another. Over the whole of the left side, face, limbs, and trunk this twitching and tremor were more marked than in the muscles of the right side. There was a spasticity of all the muscles of the body, more marked on the left side than on the right. The deep reflexes were exaggerated on the right side and absent, from spasticity, on the left side. No disturbances of sensation were found. Lumbar puncture gave a clear fluid with 25 cells, mostly lymphocytes, per cubic millimeter, and a slight haze with the Noguchi butyric acid test for globulin. Blood count and ophthalmoscopic and otoscopic examination were negative, and a negative Wassermann reaction was found in both serum and spinal fluid. No tubercle bacilli or other organisms were found in the spinal fluid. The temperature continued to swing from 99° to 101°. Two weeks after admission the spasticity, twitching, and tremors subsided, and on leaving the hospital six weeks later he had entirely recovered, except for a slight tremor of the left foot, and occasionally of the left arm, when he was tired or excited. Since then he has remained well. The character of the tremor, the spasticity and the flexed attitude of the arm and hand, together with the fact that during sleep the affected muscles became quite relaxed, suggested a lesion in the cerebellar-rubrospinal tract. The character of the spinal fluid, the comparatively rapid recovery, and the

occurrence during an epidemic suggested that the polioencephalitis might be due to the same etiological factor as acute epidemic poliomyelitis.

CASE V.—J. C., a boy, aged four years and seven months, with a satisfactory family history and a good previous history, complained of pain in the mouth four days before admission, and his lips were seen to be trembling. The next day he had difficulty in swallowing and seemed feverish, and the following day was unable to articulate or to swallow. On admission his temperature was 102.4° and after reaching 105.4° two days later, settled gradually. He was semicomatose. His face was mask-like, and he lay with head retracted and legs drawn up. The muscles all over the body were rather spastic and there were frequent clonic spasms of the right side of the face, with occasional convulsive twitchings of the arms and legs. On the day after admission the spinal fluid was clear, but contained some small white flakes and 286 cells per cubic millimeter, large mononuclear cells predominating. The cells gradually decreased in number, but the spinal fluid was not noted as normal for two months later. No tubercle bacilli or other organisms were found, and the Wassermann reactions in serum and spinal fluid were at all times negative. Except for a moderate increase in the white blood corpuscles, the examination of the blood was negative. The coma continued for nine days, and then he gradually regained consciousness and the muscular rigidity passed off. The face remained mask-like, and there was a symmetrical weakness of the muscles of facial expression on both sides. The elevators of the lower jaw were nearly completely paralyzed on both sides, the tongue was motionless except for some slight power of elevating the posterior portions, and there was no power of articulation. Saliva dribbled continuously from his mouth, and he could only swallow food when it was placed well back in his pharynx. The orifice of the fauces was wide and cavernous, and the soft palate and pillars of the fauces motionless. The right arm was weaker than the left and somewhat spastic, and showed athetoid movements and incoördination. There were no disturbances of sensation. On leaving the hospital three months later the general condition had improved very much, and the tremors, spasticity, and athetoid movements of the right arm were much less marked. When seen two months later, one side of the soft palate was active while the other was still paralyzed, and four months after that the palate had recovered, and instead of the wide, gaping aperture of the fauces, there was a small aperture with the pillars of the fauces and the soft palate quite mobile. Otherwise, little definite improvement had taken place, though he could swallow better, the saliva dribbled rather less constantly, and he made more intelligible attempts at articulation. Bilateral atrophy of the tongue was noticeable.

Prognosis. Prognosis must always be guarded in the acute stage, as muscles of vital importance may become rapidly paralyzed in the course of a few hours. It is difficult to say when the danger of further spread is over, but although cases are seen where the acute symptoms disappear only to reappear with increased severity after a few days, they are exceptional. When the fever has subsided and appetite and spirits have returned, further spread is unlikely and the prognosis as to life is brighter. A few cases run an acute course, with marked general symptoms that clear up as by crisis in a few days.

Case VI.—A boy, aged three years and eight months, complained of headache and pain in his chest, and seemed feverish for three days. He appeared to recover, but a day later the same symptoms returned. On the sixth day he was worse and seemed unable to swallow. It was thought that he had diphtheria. On admission on the tenth day of his illness he was emaciated and apparently unconscious, with marked stiffness of the neck and back and a temperature of 102.9°. The spinal fluid was clear and contained 34 cells per cubic millimeter, 95 per cent. of which were mononuclears. The face seemed a little drawn to one side, the voice was feeble, and the tendon reflexes were all exaggerated. Respirations were noisy from the bubbling of the air through the accumulation of mucus in the throat, but no involvement of the respiratory musculature was observed. During the following day the temperature rose to 103.6°, but the condition seemed otherwise the same. On the second day after admission the temperature dropped to 99.8°, and the child could talk and clear his throat, and he was eager for food. A complete paralysis of the left side of the face was the only residual involvement.

Such cases are comparatively rare, and where the acute symptoms pass off gradually it is difficult to prognosticate for some days as to whether further spread will occur or not.

The prognosis as to the ultimate recovery of power in the paralyzed parts is one of still greater difficulty. As a general rule, muscles that show the power to contract at a period when all acute symptoms have cleared up and the child is apparently well except for the paralysis will not become weaker, and can, with careful treatment, regain their power to a variable extent. If the affected muscle be one of a group of similarly functionating muscles, the others of which are active, it is more likely to recover than when all the muscles of the group are completely flaccid. This is well seen in the muscles of the shoulder girdle. The deltoid is more likely to recover if the supraspinatus and infraspinatus are active than when all the scapulohumeral muscles are flaccid. The prognosis also is better for a muscle such as the biceps if the other muscles of the arm are active than when all the muscles of the limb are completely flaccid, and there is probably a destructive

lesion involving the anterior horn cells of the lower cervical and upper dorsal segments of the cord on that side. It is important therefore, that the condition of the muscles at any time be ascertained. It is not sufficient to observe whether or not a muscle is able to perform its function, for a muscular contraction may not be sufficiently strong to move the part, and yet the muscle may not be totally paralyzed. In the legs the tendons of the dorsiflexors of the ankle can often be seen to tighten on tickling the sole of the foot, and yet no movement of foot or toes occurs, and the same stimulus may be sufficient to cause a movement in the muscle mass of the quadriceps extensor that can be felt by a hand placed gently about the thigh, but that cannot be seen or recognized by a movement at the knee-joint. If the knee be bent so that the hamstring tendons are relaxed, and the sole of the foot stimulated, contraction of the hamstrings may be recognized by a tightening of the tendons that is readily felt, although no further flexion of the knee is produced. In a similar way, action of the glutei can be ascertained by pressing with the finger-tip in the region of the gluteal fold or simply by stroking the skin in the same region; of the lumbar muscles by stimulating external to the muscle mass in the angle made by the margin of the muscles and the twelfth tib; of the vertebroscapular muscles by gently stroking the skin internal to the vertebral border of the scapula; of the scapulohumeral muscles by a similar stimulation external to the axillary border of the scapula and over the supraspinous fossa, the arm being placed in a position of partial abduction; of the pectoralis major by stimulating the inner end of the anterior axillary fold with the arm in the semi-abducted position; and of the muscles of the abdominal walls by means of the abdominal and epigastric reflexes. By similar methods of examination, other muscles that appear to be paralyzed are seen to retain some power of contraction or to have regained such power.

With the object of ascertaining whether in the early stages any prognostic value could be placed on the electrical reactions of the paralyzed muscles, 11 cases were tested. With children a general anesthetic is necessary to obtain satisfactory reactions in individual muscles, and this was not considered justifiable, so that complete reactions were not obtained, as the patients soon grew restless and impatient during the examination. It was, however, possible to test one or two muscle groups satisfactorily in the quieter patients, especially in a paralyzed limb, but in no case was it attempted until all tenderness of the acute stage was passed. The earliest to be examined was tested on the tenth day after the onset of paralysis. In this case a weakened quadriceps reacting well to faradism recovered, the calf muscles apparently paralyzed gave a weak reaction to faradism, and at the end of twelve months showed no return of power, and the anterior tibials and peronei gave no contraction to faradic stimulation, and with galvanism, kathodal

closing contraction was greater than anodal closing contraction, (KCC > ACC). At the end of twelve months the anterior muscles showed no return of power, but some atrophy. In another case a paralyzed tibialis anticus muscle gave no response to faradic stimulation when examined on the fourteenth day, and with galvanism ACC > KCC, but the response was sharp, not sluggish, as in a typical reaction of degeneration. The muscle recovered well in the course of a few weeks. Such a reaction as this was found commonly in muscles that subsequently recovered well. Typical reactions of degeneration with slow response were found in several cases where the muscles subsequently recovered to a varying extent. It is impossible to draw conclusions from the few cases tested, and it is possible that if stronger faradic stimulation had been tried than was possible in unanesthetized patients, contractions to this form of stimulation would have been obtained. It is, however, safe to conclude that muscles giving soon after onset of paralysis no reaction to strong faradic stimulation and giving with galvanic stimulation ACC > KCC may recover.

Even if a muscle is showing commencing atrophy, a partial recovery may take place and the condition of a partially atrophied but active muscle is frequently seen. The question of whether or not the bones of a paralyzed limb will grow in length as the bones of an unaffected limb is difficult to decide without a large number of cases observed over a longer period, but it seems probable that shortening may be expected in a totally flaccid limb, especially in those cases where the muscles of the limb girdle are also completely paralyzed, while no shortening will be found in a limb with only one or two muscles or muscle groups affected. The prognosis is always worse when such muscles as the deltoid and dorsiflexors of the ankle and peronei are affected, as these muscles are more resistant to treatment than any others, and even if all the muscles of a lower limb regain, at least partially, their power, it is likely that the child will always have a limp of greater or less severity. It is impossible to state a period beyond which no further return of power can be expected, especially in cases that have not received careful treatment. In one case that had received vigorous treatment since the onset a muscle thitherto showing no action began to recover at the end of two years, but in a completely paralyzed muscle recovery to any great extent can seldom be expected after a year of unsuccessful treatment.

Treatment. For the purposes of treatment, acute poliomyelitis may be divided into three stages: (*a*) the acute stage of fever and general symptoms, including the period of onset and spread of the paralyses; (*b*) the stage of recovery of muscle power; (*c*) the stage where recovery in muscle power is as complete as it is going to be, and the treatment is applied to the residual condition of deformities, flail-joints, etc. In this last stage the treatment must be surgical,

and will not be dealt with except insofar as indications for such treatment arise in the stage of recovery of muscle power.

(*a*) Apart from the suggestive work of Netter,[9] in attempting to control the acute stage by subdural injections of serum from recovered cases, no specific treatment has as yet been discovered that will check the process when it has commenced. When urotropin (hexamethylenamin) is administered by the mouth it may be detected in small quantities in the spinal fluid, and since it was suggested that this might have some power to destroy the virus of poliomyelitis it was hoped that urotropin might check the processes in the central nervous system.[10] Twenty-two cases were treated with urotropin by oral administration. Cases that were still advancing on admission or such cases that showed marked meningitic symptoms were usually treated in this way, and the administration continued only until the acute stage was passed, but in several cases the treatment was continued much longer. Doses of 0.3 gm. three or four times a day were employed in most instances for a child of two years. In one case the administration was continued for four weeks, during which time the patient, a child of three years, had a total of 16.8 gm. In two instances hematuria developed that ceased as soon as the urotropin was discontinued. In a child of two and a half years the hematuria appeared after five days, during which 5 gm. urotropin had been administered, and in a child of one year it developed on the sixth day after the patient had received 6 gm. In no instance did this treatment appear to cut short the acute stage, and in no instance was there any evidence of more satisfactory or more rapid recovery in the paralyzed parts. No decision as to the efficiency of urotropin can be reached without the statistics of a large number of cases, or by means of some precise method of estimating results.

In 1912 Clark,[11] published results of the action of intraspinous injections of epineiphrin or adrenalin in the treatment of the experimental disease in monkeys during the acute stage, in which the progress of the paralysis was stayed at least temporarily. In 8 cases in which the paralysis was rapidly developing and in which there was extreme respiratory involvement, this line of treatment was tried. The largest dose was 3.0 c.c. of a 1 to 1000 solution injected along with an equal volume of saline and washed in with 1.0 to 2.0 c.c. more of saline, but, as a rule, doses of 1.0 c.c. or 1.5 c.c. were used. There was usually a rise or blood-pressure of from 10 to 20 mm. of Hg. systolic, without any change in the diastolic pressure; the summit of this rise occurred in from twenty to thirty minutes. The increase of pressure disappeared in from

[9] Compt. rend. Soc. de biol., 1911, lxx, p. 625.

[10] Crowe, Johns Hopkins Hosp. Bull., 1909, xx, p. 102. Flexner and Clark, Jour. Amer. Med. Assoc., 1911, lvi, p. 1750.

[11] Jour. Amer. Med. Assoc., 1912, lix, p. 367. The Action of Subdural Injection of Epinephrin in Experimental Poliomyelitis.

forty-five to sixty minutes. The dose was repeated in from three to six hours, and the same rise of blood-pressure was noted. In 3 cases three doses were given. In 1 case, twitchings of the limbs came on a few minutes after each dose, in addition to the rise of blood-presure. In 2 cases it was thought that the respirations were easier and the diaphragm acting better after the injections, but such improvement was slight and transitory. Of the 8 cases, 5 died, but it is impossible to say that in the 3 cases that lived the cessation of progression in the paralysis was due to the injections.

Except in cases of respiratory involvement where the patient is fighting for breath, the child lies quietly in bed and makes few attempts to move, and complete rest is assured if care is taken to make it comfortable. The twitchings and jerkings described above and occasional turning of the head from side to side appear to be involuntary and occur most frequently during sleep or in the drowsy or comatose patients. If care is not taken to obtain a satisfactory posture, however, the child may become very restless. Whenever rigidity, resistance to anterior flexion, or definite retraction of back and neck are present, the child should be supported on its side or a pillow placed beneath the shoulders or back. Pressure on the limbs and trunk should be avoided, where hypersensitiveness of the skin or deeper structures is present, by means of a wire cradle to support the bedclothes or by the clothes being stretched from side to side of a crib, and with a heavy patient a water-bed adds greatly to the comfort. The hypersensitive condition of muscles, tendons, and ligaments makes any position of a limb that results in tension on these structures irksome, and it is found that the position of semiflexion is usually the most satisfactory. If an affected arm be allowed to be at the side, the shoulders and elbows are strained, but comfort may be obtained by means of a pad in the axilla to keep the arm from the side, and the position allows the elbow to be conveniently flexed. A pillow under the knees will in the same way obtain the semiflexed position of the hips and knees, but in most instances the child appears to be quite comfortable with the legs stretched out, and it seems to be in cases of partial involvement of the hamstrings and adductors that the flexed position is desired. The position of the foot is important, and in the majority of cases requires attention. The weight of the bedclothes, on the foot, and in many cases the weight of the foot alone, will cause an extension of the ankle in cases where the anterior tibial muscles and peronei are affected, and if this is allowed to take place for even a few days, shortening of the flexor tendons results and necessitates not only much pain in correcting the position, but has also a deleterious effect on the recovery of the stretched muscles. A light wire or other right-angled splint to support the foot and relieve the tension on the extensor muscles and tendons should be applied, or the foot simply supported in the desired position with

pillows. In the less severe cases that do not remain at complete rest the splint is preferable. In a limb that is not completely flaccid, the muscles, tendons, and ligaments seem readily to become stiff, and no joint should be kept in one position longer than is absolutely necessary. In most cases the pain and tenderness have sufficiently subsided in a few days to allow of gentle handling, and the joints can then be carefully moved. As soon as the acute general symptoms have passed off, the joints should be exercised to their full functional movements and the pain of the stiffened structures must not be mistaken for the pain and tenderness of the acute stage, since the resulting limitation of movement will be the more difficult to correct the longer the delay. If the pain is not relieved by posture, hot applications, aspirin, or opium preparations may be necessary.

The general treatment during this stage is similar to that of any acute infection. In the severe and possibly fatal cases with the respiratory involvement, diffusible stimulants were administered, and when the dyspnea became marked, oxygen was administered without any lasting benefit. Artificial respiration has been attempted when the respiratory musculature failed rapidly, but in all cases the heart failed before any return of power in the respiratory muscles appeared.

Defecation is sometimes difficult to regulate, and this is seen in cases that have weakness of the muscles of the abdominal wall, and also in cases that show no apparent impairment of the voluntary muscles concerned. Large doses of cascara, castor oil, or calomel, and saline purgatives have frequently to be followed by enemas before evacuation is obtained. Similar difficulty with micturition is seen, and catheterization may be necessary, but does not often continue for more than a few days.

Little trouble is experienced with diet. During the early days the patient will not eat solid food, but is thirsty and will take sufficient milk. As soon as the general symptoms pass off, the appetite returns and there is no indication for restricting the diet. A few cases require to be fed with a nasal tube because of the paralysis of the pharyngeal muscles, and cases where the tongue or palate is involved, require the care that similar conditions in other diseases necessitate.

In spite of careful treatment, cases with impairment of the muscles of respiration or of the upper respiratory passages may develop an inflammatory condition of the lungs that results in a fatal termination, without further spread of paralysis.

(*b*) The treatment during the second stage of recovery and return of muscle power must be based on the pathology of the condition so far as that can be ascertained. The acute inflammatory action is at an end, the edema is probably disappearing, the cells that will not recover are being absorbed, and those that are less severely

damaged are perhaps slowly recovering. The centres supplying certain muscles or muscle groups may be entirely destroyed, while in other centres most or only a few of the anterior horn cells are intact, sufficient, perhaps, to give the muscle power of voluntary contraction or sufficient, perhaps, to contract a small portion of the muscle or give the whole a feeble stimulus, but at first unable to cause the muscle to functionate in a recognizable manner. Every stage is seen between muscles that spontaneously recover in a few days and muscles that will never regain their power. No treatment is known that can hasten the resolution process in the central nervous sytem, and the muscles must, therefore, be maintained in a condition as satisfactory as possible as regards nutrition, and their control by means of the central nervous system must be encouraged. Their nutrition can be most efficiently maintained by vigorous massage and by other measures, such as hot air or water-baths that stimulate the circulation in the part. The central control can probably be encouraged most efficiently by the voluntary effort to cause the muscle to contract—that is to say, by active exercises. That electrical treatment by galvanic current can do more than act as massage is doubtful, and when the faradic current can cause contraction it would appear to be only a form of involuntary exercise due to stimuli at a point distal to the anterior horn cells, from which the voluntary stimulus is to arise. Electrical treatment may be a useful adjunct to massage and exercises, but cannot replace them. The use of high-frequency currents has been advocated,[12] even in the earliest stage, in the belief that it causes a diminution of the edema in the spinal cord, but satisfactory demonstration of its efficiency is lacking.

As soon as the acute process has subsided massage must be commenced. At first it can only be gentle and for a short period, but as the nurse or attendant gains the confidence of the child, the treatment may be increased in vigor until deep kneading of the muscle masses for twenty or thirty minutes two or three times a day can be borne. Passive movements must be performed at all the joints to prevent any limitation of movement, and it is found that if these are properly carried out from the beginning there is only in exceptional circumstances any troublesome contractures. There is danger in too vigorous application of such movements, which may stretch capsular structures and loosen joints, such as the knee or the shoulder. The active exercises must depend upon the age of the child and are most successful in the very young patients if regarded as play. A patient of less than two or three years cannot be taught to perform systematic movements, but can be stimulated to perform these movements in play. Floating toys in a warm bath provide the necessary stimulus, and the water

[12] Frauenthal, H. W., Jour. Amer. Med. Assoc., 1913, lxi, p. 2219.

gives a useful support to weakened limbs. A ball or a bright object may be used to encourage movements of an upper limb, and similar tricks may be devised for the lower limbs. The dispositions of the patients are very variable and no two children can be treated alike. Even if no movements of the limbs are seen, the stimulus must be applied and the child helped in the movements at first. The more the child tries, the more successful the treatment. With a child of over three years the intelligence is such that more systematic movements can be employed. Definite exercises against resistance must be detailed for each muscle or muscle group affected.[13] The weight of the limb may be sufficient resistance at first or it may be too great and help must be given, or it may be too little and gradually increasing pressure against the movement must be employed. Even though no movement is effected it must in all cases be attempted. After the muscles have been loosened and warmed by massage is the best time for the exercises. Before the muscle is strong enough to raise the part, a good method is to raise it passively and then allow the limb to fall slowly by its own weight, telling the child to prevent it from falling. In this way contractions of muscles can early be made effective. The spastic and ataxic conditions occasionally met with should be treated just as the flaccid condition by massage and movements passive and active.

While the muscles of a limb are recovering they regain their power at different rates, and in the majority of cases are not equally paralyzed at the commencement of the recovery, so that it frequently occurs that one muscle is capable of strong contraction while the antagonizing muscle or muscle group is still feeble. Contractures of the stronger muscles and tendons and stretching of the weaker will result, and this may tend to deformities that require operative interference if not corrected early. Stretched muscles do not recover as readily as relaxed muscles, and it is therefore important to be on the watch for such conditions and to prevent the stretching and contractures. Passive movements may be sufficient if the difference in the strengths of the muscles is not great. Splints are frequently necessary. This is well seen in the case of the ankle. When the muscles of the leg are completely flaccid the weight of the foot is sufficient to cause severe drop, but if the calf muscles are active the drop will be more difficult to prevent. The foot must therefore be fixed in the position of dorsiflexion by means of a light wire or other posterior right-angled splint or by strapping with adhesive plaster as employed by Herrick.[14] It may be sufficient to have it fixed during the night only, and free to move and exercise during the day, or it may be necessary to keep it fixed day and night, the splint being removed only when

[13] Wright, Boston Med. and Surg. Jour., October 24, 1912. Muscle Training in the Treatment of Poliomyelitis.

[14] New York Academy of Medicine, Surgical Section, March, 1914. (Not yet published.)

massage is to be given and the part exercised. A plaster cast or other splint that cannot be removed for treatment is to be avoided. In any situation where weakened muscles are liable to be stretched the position of the limb should be altered and maintained by suitable support. The deltoid is peculiarly situated, in that the arrangement of the origin and insertion necessitates a considerable power of contraction to raise the weight of the limb. A degree of weakness that would allow of functional movement in another muscle will give the effect of a total paralysis in the deltoid, and the return of power must be considerable in the deltoid before the abduction of the arm can be effected. The arm hangs by the side and the deltoid is kept on the stretch, a condition inimical to recovery. It is difficult to obtain the support necessary short of surgical interference such as that employed by Bartow.[15] A light splint made of poroplastic, moulded to the chest, axilla, and upper arm, is effective in many cases. Supporting the arm by means of such a splint in the position of partial abduction relieves the muscle and places it in a position more advantageous for functional movement, but is unsatisfactory in that it does not relieve the drag on the capsule of the joint. Care must be taken that with active adductors and stretched capsule and deltoid the splint does not act as a fulcrum to force the head of the bone from the glenoid cavity and still further stretch the weakened structures. While the patient is still in bed, a soft pad in the axilla is sufficient support.

Attention has frequently been drawn to the crippling results of paralysis of the deltoid muscle and to the small extent to which recovery takes place in the case of this muscle. In 30 of our cases, one or both deltoids were noted as paralyzed completely or partially. In 16 cases the condtion was bilateral and in 14 one or the other muscle only was affected, and of the forty-six muscles affected, thirty-six were noted as completely paralyzed; 9 of the 30 cases died during the acute stages or were lost for observation immediately after, and of the remaining 21 cases there were 28 deltoids available for observation. Of these twenty-eight deltoids that were observed for three or four months after the onset, 15 were carefully supported from the first, and of those two only showed no improvement at the end of that period, while of the thirteen unsupported muscles, five showed no improvement at the end of the same period.

Weakness of the extensors of the ankle and the resulting drop-foot is as difficult to affect by treatment as weakness of the deltoid, and is a source of trouble not only in the disability it causes, but also that the leg is swung out and externally rotated when the child walks, to avoid the drag of the toes. This may cause tilting of the pelvis and lateral curvature of the lumbar region of the spinal column. Ambulant braces will correct the drop, but are often so

[15] Shoulder and Arm Paralysis of Poliomyelitis, New York Med. Jour., 1913, xcvii.

heavy that the weakened limb swings as before, and the tilting and curvature again result. The question of braces is one of much practical difficulty. If a child can walk without deformities resulting from the weight of the body acting on a weakened limb, a brace is unnecessary. If the patient is unable to support the body weight properly, without causing deformities, he should be kept off his feet as much as possible, and by means of massage and exercises against resistance the muscles should be encouraged to regain their power. The muscles will continue to improve for two or three years at least. In many cases a child cannot and should not be prevented from walking before the legs are strong enough to maintain the body weight without deformities resulting, and then some support is necessary for the joint or joints involved. The heavy ambulant braces usually applied are often unnecessarily extensive, and their weight is extremely hampering, and instead of being applied only when the child walks, they are kept on constantly so that the exercises necessary for the development of the power in the muscles are impossible, and the ultimate result is not so good.

When a child with lower limbs affected has so far recovered that they can support the body weight satisfactorily, but walking is hampered because of the foot-drop, an elastic strap from the dorsum of the shoe and fixed below the knee to a garter or to some convenient garment is sufficient to support the ankle and allows of the leg being moved forward without the swinging and tilting movement. In many cases faulty movements, such as external rotation of the thigh, are developed in the earlier attempts at walking, probably because of excessive action of the external rotators over the gluteus medius and gluteus minimus and other muscles that cause internal rotation. If care is taken during the further recovery to direct the child's attention to this fault and to urge it to swing the foot straight, the tendency to external rotation as an accompaniment of flexion disappears. The older the child the more its efforts can be utilized and directed toward a satisfactory prevention of deformities and faulty movements, and it is in the early stages of recovery that such directed effort will be most efficacious. Striking contrasts are seen between the results obtained when the mother or attendant appreciates the requirements and when the directions are carried out without proper understanding of these requirements.

The muscles of limbs and trunks can be treated effectively by massage and exercises, but those of the face, pharynx, tongue, etc., can only with difficulty be reached by such methods. These muscles, however, are so situated that they are being continually exercised and massaged by the movements of the neighboring parts, and they are continually receiving stimuli for active movements, so that further treatment seems unnecessary. The muscles of the face are amenable to electric treatment, and though it is difficult

to draw conclusions as to the relative efficacy of treatment, cases treated electrically do not appear to recover more rapidly than those that are let alone. Because of the fact that cases are seen showing every stage in rapidity of recovery from the muscle that regains power in a day to the muscle that regains no power and progressively atrophies, it is peculiarly difficult to judge of what effect, if any, the treatment has had, the more so since muscles that for months show no voluntary movement and commencing atrophy will even then commence to recover in cases that have received no treatment. No two series of cases are quite comparable, since epidemics vary in severity not only as to fatality, but as to localization and severity of paralysis. Treatment must, therefore, be directed along lines that follow the indications of the pathology of the disease and that are most likely to prevent crippling and deformities. The conditions vary in each case, but by following the indications to maintain the nutrition of the muscles, to encourage movement and to prevent deformities, and by carrying out such treatment energetically, carefully and logically, much of the crippling effects of the disease can be prevented.

GALL-STONES VIEWED FROM A SURGICAL STANDPOINT.

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In considering the subject of gall-stones from a surgical standpoint, we are concerned equally with the internist in the consideration of the etiology, inasmuch as the conditions which determine their origin must likewise be important factors in their recurrence after operation. Until recently the dictum of Naunyn has been accepted, namely, that with stasis of the bile in the gall-bladder there occurs an infective inflammation of its lining membrane, and under these conditions only does the precipitation of cholesterin take place. A notable contribution to our knowledge on this subject is the work on cholelithiasis by Aschoff and Bacmeister. Therein it appears that the solitary gall-stone has a different composition than have multiple gall-stones. The former is composed of pure cholesterin, usually with a nucleus of pigment. The cholesterin is arranged in radiating rods. There is no lamination. This form of stone is found in non-infected gall-bladders, and arises therefore without preëxisting inflammation. The multiple stones are laminated and are of mixed character, containing cholesterin, lime salts, and pigment. These are always the result of an infective

process. However, the pure cholesterin stone may provoke sufficient irritation in the gall-bladder to subsequently arouse an infective inflammatory process, and resulting therefrom multiple stones may form. Whatever may be the explanation, women are much more susceptible to gall-stone disease than men. The pressure of their clothing and pregnancy are by some considered responsible, while the character of food and constipation are regarded as etiological factors. Aschoff and Bacmeister hold that dropsy of the gall-bladder always depends upon a previous inflammatory process. Their work is based upon the thorough pathological examination of 250 gall-bladders which had been excised because of the inflammatory changes in them. Fifty other gall-bladders removed from dead bodies were likewise subjected to their careful investigation.

In determining the source of infection of the gall-bladder, investigation has proved that it may be either of ascending or descending character. The organisms are those usually found under normal conditions in the intestinal tract. Thirteen minutes after Kraus made an intravenous injection of bacteria, he was able to demonstrate their presence in the hepatic duct. It is well known that in the early stages of typhoid fever the bacilli are present in the blood. These bacilli may find their way into the bile through the blood-stream or may enter the bile-current through the excretory function of the liver, or they may ascend from the intestines through the common duct and thus find their way into the gall-bladder. Other infective processes, like pneumonia, influenza, and erysipelas, have been known to provoke cholecystitis. Naunyn injected virulent bacteria into a normal gall-bladder where their motility was nowise disturbed, and they disappeared after a short time.

Gall-stones can provoke infection of the gall-bladder in various ways: (1) the mucous membrane may be lacerated by a stone; (2) a stone may by pressure interfere with the circulation; (3) the obstruction may cause stasis of bile; (4) bacteria may be present in the gall-stones.

Cancer of the gall-bladder was found by Aschoff and Bacmeister in 9 cases. Of these 2 presented radiating stones. Evidently in these the stone was primary and the malignant process secondary. In 5 the stones were multiple and of the mixed type. In these it was impossible to determine whether the cancerous invasion was primary or secondary. In 2 cases of cancer of the gall-bladder no stones were found.

Körte in discussing the relation of cancer to gall-stones established three groups of cases. The first included patients who for years had symptoms of gall-stones which finally merged into those suggestive of cancer. In the second group he placed those who having had symptoms of gall-stones, presented a long period of quiescence, after which came the manifestations of cancer. In the third group there had been no previous symptoms of gall-

stones whatsoever. Of the 32 cases, 14 belonged to the first, 10 to the second, and 8 to the third group.

Referring again to infective processes which may involve the gall-bladder, it should be emphasized that cholecystitis may occur without the presence of gall-stones. It may be an acute complication of typhoid fever. However, its occurrence as a sequel of typhoid fever does not necessarily establish a causal relationship. In a case of cholecystitis, which occurred a month after the termination of an attack of typhoid fever, presenting the usual acute abdominal symptoms—namely, pain referred to the right hypochondrium, marked tenderness, localized rigidity, and the presence of a tumor, but without biliary colic—at operation an inflamed gall-bladder was found greatly distended and adherent to the pyloric end of the stomach. The inflammatory contents contained the pneumococcus, but no typhoid bacilli.

While gall-stones are ordinarily formed in the gall-bladder, they may originate in the biliary route, According to Adami, gall-stones are most frequently found in the gall-bladder, next in the cystic, then the common duct, and least frequently in the hepatic duct.

With an infective process established in the gall-bladder, various changes can occur. The gall-bladder may become greatly distended. In one of my cases it reached well below the level of the umbilicus and contained over a quart of fluid. The virulence of the infection may destroy the lining membrane and even lead to gangrene and perforation of the gall-bladder with localized or general peritonitis. The infectious process may spread to the surrounding structures and produce marked adhesions to the pylorus and duodenum. Sometimes the adhesions serve as a protection so that a perforation of the gall-bladder into the duodenum can result. An opening of sufficient size may be established to permit the passage of gall-stones directly into the duodenum and cause intestinal obstruction. These stones usually pass down to the lower part of the ileum and become fixed at or within a few inches of the ileocecal valve. A mass of such dense hardness is found that it suggests carcinoma. The clinical picture of chronic intestinal obstruction is presented. Many times no preceding manifestations had occurred to arouse a suspicion of gall-stone disease, and the finding therefore has been entirely unexpected.

Mixed infections occur at times, causing hemorrhagic septicemia. Twice the writer has seen the body covered with purpuric areas, and even extensive ecchymosis, each time in advanced and neglected cases of gall-stone disease. The tendency to hemorrhage in cases of persistent jaundice is too well known to require more than reference to it.

Adhesion to the peritoneum and to the structures mentioned may lead to distortion of the gall-bladder and kinking of it. In conse-

quence there may be sufficient interference with the passage of bile to cause biliary colic. It is because of these adhesions that patients frequently suffer after gall-bladder operations, the suffering assuming the same type and the symptoms being of the same kind as when they had true gall-stone colic.

The varying pathological conditions with which the surgeon has to deal explains the incongruity of the clinical picture. The most frequent symptom of gall-stone disease is biliary colic. Its production depends upon the free admission of bile into the gall-bladder and the temporary interruption of its discharge into the common duct because of the presence of a stone or other obstruction. If the gall-bladder becomes entirely filled with gall-stones, bile sand, or a putty- or clay-like material, so that these substances are fixed within its cavity, the patient may never experience biliary colic.

The gall-bladder normally does not hold more than an ounce of fluid. Mayo has pointed out, therefore, that it cannot serve as an organ of storage. As there is secreted each day from thirty to fifty ounces of bile, the capacity of the gall-bladder is utterly insufficient to serve such a purpose. Evidently, therefore, its function is to relieve the tension upon the common and hepatic ducts as well as of those which lead to the pancreas. It likewise secretes a quantity of mucus which has a definite physiological purpose in serving to reduce the probability of occurrence of pancreatitis or other complications. When more or less complete obstruction in the cystic duct occurs, and the contents of the gall-bladder fail to find an outlet, the fluids within this sac become absorbed and the gall-bladder contracted. In the end we frequently find it so small, and when packed full of stones so hard and dense, that it can only be a source of irritation. The opening of the pancreatic ducts at the ampulla of Vater favors the extension of the infectious process to the pancreas, and hence subacute or chronic pancreatitis is a frequent complication of gall-stone disease. The appreciation of its occurrence is essential in determining the indications for surgical operation.

In a recent paper by W. J. Mayo, based upon his experience and that of his associates, in which he reviews 4000 operations on the gall-bladder and biliary passages, he reaches the conclusion that the mortality associated with this condition is due to the complications incident to the disease and resulting from delay rather than the removal of the gall-stones. He shows very clearly that the death rate is greatly increased when the disease has been allowed to advance until the deeper biliary passages, liver, pancreas, and the neighboring viscera become involved in infectious processes or adhesions. On the other hand, the early removal of gall-stones from a gall-bladder not otherwise affected is an innocent and simple operative procedure. The surgeon has been taught by experience that the incision and drainage of the gall-bladder is, generally

speaking, a wiser step than is the excision of the organ. The particular reason for this is that not only can the gall-bladder be preserved and serve the function for which it was intended, but that continued drainage leads to a cure of the diseased condition which may exist in the pancreas and removes infection from the biliary passages.

As much of the disturbance which has followed operations on the gall-bladder has been due to traction of adhesions, kinking of the gall-bladder, or biliary channels, it is wise in establishing the drainage to guard against fixed adhesions. Although it has been proved that a gall-bladder fastened to the peritoneum, if it does not produce marked traction or kinking, does not lead to the reproduction of gall-stones, the tendency of recent years has been to drain the gall-bladder without anchoring it. Nearly all of the suffering which occurs after gall-bladder operations, which is frequently taken for a recurrence of the gall-stones, is due to these adhesions and the consequent displacement of the biliary channels. That these conditions can occur without the presence of gall-stones is evidenced by the fact that we frequently encounter patients who have apparently suffered from cholelithiasis, but upon opening the gall-bladder we find either an hour-glass constriction of the gall-bladder or adhesions about this structure and no gall-stones. Recently I operated upon a patient who had passed gall-stones freely for a number of years. The gall-bladder was in a state of chronic inflammation, and had numerous diverticula, but a careful search did not discover a single gall-stone. All of the manifestations evidently had been kept up by the adhesions.

The frequent association of disease of the gall-bladder and the appendix is known to all surgeons. Gall-stones may remain latent and may not have provoked any manifestations until an infectious process in the appendix or elsewhere in the abdomen has awakened a secondary infection in the gall-bladder. This should not surprise us when we remember that only a small percentage of the people having gall-stones suffer therefrom. Autopsy reports show that 10 per cent. of all bodies present gall-stones, and of this large number 95 per cent. never had any manifestations suggesting the presence of gall-stones during life. The surgeon today, therefore, examines the gall-bladder as a matter of routine in every opened abdomen.

A movable kidney can be responsible for the symptoms of gall-bladder disease. Treves has reported cases in which a movable kidney has produced pressure upon the cystic duct interfering with the passage of bile from the gall-bladder and provoking symptoms of biliary colic which were relieved by fixation of the kidney. On the other hand a movable kidney may become fixed at the site of the gall-bladder, and if it become infected may strikingly resemble cholecystitis. This was illustrated in a case presented at the writer's clinic a number of years ago, in which the patient had been

acutely sick for a few days. Her temperature was above 104° at the time of her admission. She had a large tender tumor in the right hypochondrium, reaching down to the umbilicus, which was tense, fluctuated, and occupied the normal position of the gall-bladder. With an aspirating needle pus was withdrawn. Upon opening the pus sac it was found to be made up of a series of compartments, and was recognized as a pyonephrosis. After the infectious process had subsided a urinary fistula formed which persisted for some time. Similar cases have been reported by other surgeons.

We can best illustrate the points we desire to emphasize by presenting briefly the histories of a few cases taken from our clinical records.

CASE I.—*A typical case of single gall-stone producing obstruction to the outflow of bile and resulting in cholecystitis.*

The patient was a woman, aged forty-three years, seen in consultation with Dr. Sears, December, 1902. Eight years previously, while a patient at Mt. Sinai Hospital, she was told that she had gall-stone disease. An operation was advised, but was declined. For the five months preceding my consultation, the patient, having been free from manifestations for a number of years, had recurring attacks of pain, each lasting from several days to a week. These would begin in the epigastrium and extend to her back. She was admitted into St. Joseph's Hospital, February 28, 1903, at which time an elastic tumor could be felt in the right hypochondrium, which apparently could be moved laterally and was moderately tender. There was slight rigidity of the upper portion of the right rectus muscle. On March 2 I operated upon her at my clinic and found a single gall-stone about an inch in length and three-quarters of an inch in width. The tumor which we had been able to palpate proved to be a Riedel's lobe of the liver. The gall-bladder presented extensive adhesions. The patient made an uninterrupted recovery, and now after ten years has had no recurrence of the trouble. This case is typical of the disturbance caused by a single movable stone associated with a mildly infectious cholecystitis.

CASE II.—*Gall-stone impacted in the gall-bladder at its cystic end, producing acute gangrenous cholecystitis.*

The patient, a woman, aged forty-three years, was seen at her home in Elbridge, November 3, 1907, with Dr. Kaple. Prior to that illness she had experienced attacks of severe abdominal pain without fever which would last never longer than a day. Five days before she was seized with general abdominal pain, which became fixed in the right side. Her temperature ranged from 99.5° to 101°. At the time of my examination the pulse was 100, temperature 101°, and there was leukocytosis of 33,000. Tenderness was present in the right upper quadrant of the abdomen, where there was also an increased area of dulness which reached almost to the level of the umbilicus. There was marked rigidity, but no jaundice.

An incision was made through the right rectus, and ptosis of the liver was found. The gall-bladder was dark, swollen, and tense. Upon incision a gall-stone an inch and a half long was found wedged into the cystic duct. The entire mucous lining of the gall-bladder was gangrenous, and was easily removed. The gall-bladder was drained. The patient made an uneventful recovery.

CASE III.—*Gall-stones with cholecystitis, causing frequent and acute exacerbations for a number of years; operation deferred until the occurrence of rupture of the gall-bladder.*

The patient was seen first by me March 20, 1904, with Dr. Levy. The attacks of gall-stones colic had been characteristic. On one occasion there had been associated jaundice. The pain had each time been very severe. In different attacks he had been seen by various physicians, all of whom had concurred in the diagnosis and had recommended operation. Early in 1905, after a severe attack he agreed to go to the hospital, but he failed to report for operation. On December 15, 1906, he became prostrated with the most severe attack he ever had had. Three days later he was admitted to St. Joseph's Hospital. At that time he had a pulse of 120, temperature 102°, and was jaundiced. The abdomen was distended and generally rigid. Because of the evident general peritonitis, operation was deferred, with the hope that under rest, the exclusion of fluids, and the administration of the Murphy drip the infection might become localized. The urine contained both albumin and casts. The temperature began to subside and the rigidity and dulness were restricted to the right hypochondrium; but he grew so nervous and seemed to be possessed of such fear of an operation that he was unable to sleep or to control himself. On December 26 I operated upon him. The omentum was adherent to the liver and the intestines. The gall-bladder had been ruptured. The exposed area was occupied by structures which had become matted together by the infectious process. One large space was found which contained a quantity of bile, and in this way the lower border of the liver was finally found, and what remained of the gall-bladder was seen. It was a gangrenous mass, and thick yellow bile was pouring out of it. A rubber drainage tube was introduced and the area packed off with gauze. The patient's condition on the table was not satisfactory. He rallied and seemed better later in the day, but the improvement was only temporary. The urine became entirely suppressed. The temperature rose to 105°. He had a series of severe convulsions, and died about forty hours after the operation.

CASE IV.—*Gall-stones after causing repeated attacks of biliary colic became latent for ten years, when acute cholecystitis developed as a complication of typhoid fever.*

The patient, a woman aged thirty-four years, was seen at her home in Oswego in consultation with Drs. Elsner and Eddy, November 7, 1904. Up to ten years previously she had had repeated attacks

of biliary colic, but none again until her present sickness. She was in the third week of an attack of typhoid fever, when she was seized with a chill and severe pain in the right hypochondrium. Dr. Elsner was called to see her and found a large tender mass in the right upper quadrant of the abdomen. During the night a quantity of gritty bile sand was discharged per rectum. There was a slight reduction in the size of the mass and moderation of tenderness. Jaundice was present. The urine contained a trace of sugar. At the operation the omentum was found adherent to the gall-bladder. Four ounces of fluid were withdrawn from this sac. The first of it was watery and the latter portion purulent. The gall-bladder was opened. Fifteen gall-stones were removed, of which eight were large. No bile sand was found. The gall-bladder was drained. The patient made an uneventful recovery, and has remained well since.

CASE V.—*Gall-stones causing cholecystitis, chronic pancreatitis, and toxic nephritis.*

A woman, aged thirty years, married but never pregnant, had her first attack of gall-stone colic six years previously. She was referred to me November 21, 1906. At that time she had been suffering from an attack which had been of five weeks' duration. The pain had been constant. She had no fever. She had persistent jaundice. There was tenderness over the gall-bladder, but no definite tumor. The urine was dark, sharply acid, had a specific gravity of 1032, contained 2 per cent. of albumin, 2½ per cent. of sugar, and hayline and granular casts. Dr. Coon made three exposures for the purpose of taking *x*-ray pictures. Disturbance in the region of the gall-bladder was indicated in these plates, but a definite diagnosis could not be made therefrom. At the operation the gall-bladder was found adherent to the surrounding structures, and the adhesions were too dense to be separated. A single stone was found in the gall-bladder. The pancreas was hard and dense. Drainage was continued for three weeks, at which time the urine had become free from albumin and sugar and the granular casts had disappeared. The patient made a complete recovery, and has remained well since.

CASE VI.—*Gall-bladder filled with inspissated bile, bile clay, and gall-stones without causing any manifestations until within ten days of operation, when acute cholecystitis developed.*

A woman, aged fifty years, was sent to St. Joseph's Hospital, September 20, 1903, by Dr. McKenna. She had suffered from frequent and severe headaches, but had had no particular abdominal discomfort until a week prior to the date of her admission. She attributed her gastric distress to indiscretion in diet. For five days she had had increasing abdominal pain. She complained of difficult breathing. The pain was constant, not of colicky character, and was referred to the right side of the abdomen above the level of the umbilicus. On admission her pulse was 96, temperature 100.6°.

There was an apparent prominence to the right of the median line, midway between the umbilicus and the ribs, about the size of a small orange. It was tense and tender, and could be moved from right to left. She had been given a dose of castor oil the night before, and the bowels moved freely. The stools were watery. During the next forty-eight hours the temperature remained stationary, namely, about 100.5°, but the mass increased steadily in size, and rigidity of the overlying muscles became apparent. The blood examination showed 68 per cent. of hemoglobin, 3,800,000 red cells, and a leukocytosis of 19,000. On opening the abdomen, September 23, namely, ten days after the first manifestations, the tumor was found to be a distended gall-bladder presenting a plastic exudate, which made it particularly adherent to the liver. Upon incising the gall-bladder, several ounces of a thick mucoid substance were discharged. The gall-bladder was filled with a grumous substance, which was firmly packed in it, but was washed out by means of a stream of sterile water. This material was like soft clay, and embedded in it were twenty-eight stones. No other involvement of the biliary tract was apparent. Drainage was introduced. The patient made a satisfactory recovery, and has remained well since.

CASE VII.—*Gall-bladder and cystic and common ducts filled with gall-stones and clay, never having caused biliary colic; jaundice persistent for seven weeks prior to operation.*

This patient, a Catholic priest under the care of Drs. Muench and Larkin, was referred to me December 28, 1911. He was forty years of age. For a number of years he had suffered from indigestion. During the previous summer, gastric distress was marked. At no time was there characteristic biliary colic. A day or two after his admission into the hospital he developed jaundice. Upon exposing the gall-bladder it was found to be contracted. It was filled with gall-stones that were set firmly in the biliary clay. There was no fluid in the gall-bladder. The cystic and common ducts were equally impacted. The gall-bladder was fixed by adhesions too firm and dense to be separated. Sixty-eight stones were removed, as well as a large quantity of clay. The greatest difficulty was experienced in clearing out the common duct. Despite the jaundice, the hemorrhage at the operation was trivial. Drainage of both the gall-bladder and common duct was established. Uninterrupted recovery and complete restoration to health followed.

CASE VIII.—*Gall-stones; cholecystitis; thirty-three stones removed from the gall-bladder; one embedded in the cystic duct likewise removed; prompt healing of the wound; early recurrence of the manifestations; second operation performed four months later and a stone found in the common duct; choledochotomy.*

The patient, a woman, aged forty-eight years, had suffered from recurring attacks of pain in the region of the gall-bladder extending

to her right shoulder. The more recent attacks had been associated with jaundice, clay-colored stools, and dark urine. There was increased rigidity over the upper half of the right rectus and a moderate area of dulness. She was referred to me by Dr. Elsner, and operated February 10, 1903, at the Syracuse Hospital for Women and Children. Upon exposing the gall-bladder it was found embedded in a mass of adhesions. Two drams of light-colored serum were withdrawn. No free bile was found in the gall-bladder. Thirty-three stones were removed from the gall-bladder and one which was impacted in the cystic duct. Upon its removal the bile flowing freely. At this time the common duct was examined and no stone found in it. Soon after leaving the hospital she began to have a recurrence of manifestations. There was pain associated with jaundice. Albuminuria was present. The bowel movements had normal color. On June 17, 1903, I operated upon her again; this time at the City Hospital of Watertown. No stones were found in the gall-bladder or the cystic duct, but one was discovered in the common duct near the duodenum. The duct was incised and the stone removed. She suffered from cholangitis following the operation, but despite this condition made a recovery, and has remained well since.

CASE IX.—*Gall-stones embedded in a contracted gall-bladder; cholecystectomy.*

On February 8, 1909, a man, aged forty years, who two years previously had been under the treatment of Dr. Heffron for chronic diarrhea and colitis, gave a history of having had for two and a half years attacks of pain in the right upper quadrant of the abdomen, which recurred every three months. With some of these attacks he became jaundiced. On physical examination a tumor was found at the site of the gall-bladder extending almost to the level of the umbilicus. It was tense and hard. There was still associated colitis. He was operated upon February 19, 1909. The presenting tumor was found to be a Riedel's lobe of the liver. Beneath it was a small hard gall-bladder containing no fluid. The gall-stones filled its entire lumen. The cystic duct was clamped and the gall-bladder stripped out without opening into it. The man made an uneventful recovery.

CASE X.—*Gall-stones in the gall-bladder, and cystic and common ducts; persistent jaundice; extensive hemorrhagic areas upon the surface of the body; uncontrollable hemorrhage following operation; fatal ending.*

Patient, aged fifty-nine years, was brought to me May 16, 1905. Fifteen years before she had had what was called bilious fever. Five years before she had suffered from neurasthenia, which was characterized by great weakness, dizziness, pain in the head and neck, sensitiveness of the spine, and inability to do the ordinary housework required of her in her home. When her last illness

began ten weeks prior to her consulting me she complained of aching and tenderness of the dorsal spine, inability to concentrate her mind upon the work she had been accustomed to do daily. Soon after this time she had intermittent abdominal pains, which were thought to be due to indigestion. Later still the abdominal pain grew more severe, making sleep impossible. There was no vomiting. Gradually deepening jaundice appeared. For eight weeks she had been profoundly jaundiced. During this period she suffered from itching of the skin, an irritating cough, excessive nervousness, nausea, and intestinal fermenation. She had to be brought to the hospital a long distance on a cot. On admission a number of large ecchymotic spots were found on her thighs and buttocks. In the right hypochondrium was a mass which extended to the level of the umbilicus. It was about five inches in its transverse diameter. Her temperature was 99°; pulse, 80. Upon exposing the abdomen the mass was found to be a Riedel's lobe almost purple in color. The liver was turned up and the presenting gall-bladder was yellowish in color and about ready to rupture. Upon aspiration five ounces of pus were withdrawn. A large number of gall-stones were removed. Some were also removed from the cystic duct, while the common duct was found to be thickened. There was reason for suspecting that this thickening might be malignant. A flexible probe was carried through the duct into the duodenum. At the operation there was little bleeding. She had been given chloride of lime before the operation, and this was continued per rectum subsequently. On the day following operation the dressings were found stained with blood. A clot of considerable size was found about the tube which drained the gall-bladder. The bowel movements were darkly colored. Uncontrollable oozing, which developed into quite free bleeding, occurred. Adrenalin, strychnine, and chloride of iron as well as chloride of lime were administered. Suppression of urine followed. There never was a rise of temperature Persistent vomiting appeared. The patient died on the third day after operation.

1. Conclusions. Gall-stones can exist through life without provoking any manifestations.

2. Single gall-stones form frequently without infection.

3. Multiple gall-stones are usually dependent upon a preëxisting cholecystitis.

4. The typhoid bacillus, the pneumococcus or the streptococcus can awaken acute cholecystitis in a gall-bladder containing stones.

5. Gall-stones can by traumatism, pressure, or interference with the biliary current cause cholecystitis.

6. As a result of inflammation of the gall-bladder, adhesions form, distorting the biliary route and changing the normal configuration of the gall-bladder.

7. Perforation of the gall-bladder may occur, causing localized or general peritonitis.

8. Through the perforation, a gall-stone may pass of sufficient size to cause intestinal obstruction.

9. Cancer of the gall-bladder may be a sequel of gall-stones.

10. As a result of infection hemorrhagic septicemia may occur, or because of the persistent jaundice, hemorrhages may arise or the character of the blood may become so altered as to interfere with its coagulation.

11. Gall-stones are not harmless tenants of the body.

12. With the definite evidence of their presence, surgical attention is required.

13. Early operations are attended with little danger, and the removal of gall-stones from a bladder followed by drainage promises permanent relief.

14. Neglected cases yield poor results, and fatal termination follows operations performed at the eleventh hour.

A CRITICAL STUDY OF LANGE'S COLLOIDAL GOLD REACTION IN CEREBROSPINAL FLUID.

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Lange,[1] in 1912, described the action of cerebrospinal fluid in various conditions upon a colloidal gold solution. He demonstrated that the reaction could be used as a delicate test, differentiating normal from pathological cerebrospinal fluids, and more particularly syphilitic from other affections of the central nervous system. Zaloziecki,[2] Jaeger and Goldstein,[3] Grulee and Moody,[4] and Eicke[5] have confirmed the value of the test.

The theory of the reaction is based upon the following observations made by Zsigmondy in the course of this study on metallic colloidal solutions.

1. Solutions of electrolytes precipitate colloidal gold.

2. Proteins in the absence of an electrolyte also precipitate a solution of colloidal gold.

[1] Berl. klin. Woch., 1912, No. 19, p. 897; Zeitsch. f. Chemotherapie, 1912, vol. 1, No. 1, p. 44.
[2] Deutsch. Zeitsch. f. Nervenheilk., 1913, vol. xlvii and xlviii, p. 783.
[3] Zeitsch. f. d. Ges. Neurol. u. Psychiat., 1913, vol. xvi, Nos. 1 and 2, p. 219.
[4] Jour. Amer. Med. Assoc., 1913, vol. lxi, No. 1, p. 13.
[5] Münch. med. Woch., 1913, No. 49, p. 2713.

3. Proteins in the presence of an electrolyte inhibit precipitation in colloidal gold solutions—the so-called "Gold-Schutz."

The relation existing between this opposed reaction of electrolyte and protein is definite for the same protein, but differed when a different protein is used, and is therefore a specific property of the individual protein.

Lange first applied these principles to the investigation of sera, but the results were without significance. In spinal fluids, however, he found differences between normal and pathological specimens, when he varied the Zsigmondy technique by decreasing the concentration of the NaCl solution to 0.4 per cent., a concentration which in itself would have no effect upon the colloidal gold, but sufficiently strong to prevent the precipitation of globulin and nucleoproteins, both of which substances often occur in pathological spinal fluids.. This latter technique was also used in the study of sera, but no consistent changes were observed in pathological or normal sera.

Briefly the Lange theory is (1) That substances in pathological spinal fluids will precipitate colloidal gold provided the globulin and nucleoprotein fractions are held in solution with a 0.4 per cent. sodium chloride solution, and (2) that there is a characteristic change for certain diseases involving the central nervous system.

The technique is comparatively simple and requires the following materials:

1. Double distilled water, free from protein substances and rubber extractives.

2. One per cent. solution of gold chloride (Merck) in double distilled water.

3. Two per cent. solution of potassium carbonate (Baker & Adams Chemical Company) in double distilled water.

4. One per cent. solution of formalin (commercial) in double distilled water.

5. Ten per cent. solution of sodium chloride in double distilled water.

6. Jena beakers of 1500 c.c. to 2000 c.c. capacity (preferably the tall form).

7. One 1 c.c. pipette. graduated in hundredths and four or five 10 c.c. pipettes.

At first we encountered considerable difficulty in preparing the "reagent." In spite of every precaution to duplicate the technique poor reagents occasionally resulted. Various factors which might influence the change to the colloidal state were separately studied. We found very rapid heating was apparently an important essential. We believe that the preparation of a good, translucent, "high red" reagent with a slight blue nuance which does not precipitate on standing is largely dependent upon freeing the distilled water from the gases in solution.

Our method is to heat 500 c.c. of doubly distilled water in a Jena beaker to 60° C., add 5 c.c. of the gold chloride solution, and follow with 5 c.c. of the 2 per cent. potassium carbonate solution. As the heating continues two types of bubbles are noticed: (1) those which come from the bottom of the beaker and are moderately large, and (2) those which arise generally throughout the liquid and are at first very small and gradually increase in size, and finally disappear after one or two minutes of boiling. As soon as these latter bubbles cease to arise the flame is withdrawn and 5 c.c. of the formalin solution are added. The beaker is given a rotary motion to aid in the rapid diffusion of the formalin. It is our experience that unless the color change is almost instantaneous the resulting reagent will be poor. By following this technique we have been able to secure reagents that are macroscopically identical. This reagent can be made up in considerable quantity, and apparently lasts indefinitely.

The technique of setting up the test is as follows: A suitable amount of 10 per cent. salt solution is diluted with double distilled water, so that the resulting strength is 0.4 per cent. For a single test a row of ten test-tubes, chemically clean, are placed in a rack and 1.8 c.c. of the 0.4 per cent. salt solution are added to the first tube and 1 c.c. to each of the succeeding tubes; 0.2 c.c. of spinal fluid, free from bacterial contamination, hemoglobin admixture, or red-blood corpuscles is added from a 1 c.c. pipette to the first tube. Thorough mixing is secured by pipetting in and out two or three times, and 1 c.c. is removed from this tube to the second, which is mixed in the same way. One c.c. is removed from the second tube and placed in the third tube, and so on until the ten tubes are treated in the above manner; the last tube will have 2 c.c. in it; 1 c.c. is withdrawn and rejected. In this way the dilutions are increased by geometrical progression, in the order 1 to 10, 1 to 20, 1 to 40, and so on up to 1 to 5160. After the specimens to be tested have been treated in the above manner, 5 c.c. of the reagent are added to each tube, which is shaken immediately after the addition. Although the change is very pronounced in many instances within a few minutes after the addition of the reagent, the readings are much more distinct when taken twelve to twenty-four hours after the test is set up.

In pathological fluids the change in color of the reagent is gradual in the series. A single tube showing marked change is always to be regarded with suspicion. Such tests are always repeated, and the usual result is uniformly graded reactions. Specimens from cases which have been receiving salvarsanized serum intradurally are excepted. Tests showing a change in only one tube upon repetition are usually found to be negative.

The success of the test depends upon (1) the use of scrupulously clean glassware; (2) accuracy in all measurements (for this reason

the same 1 c.c. pipette is used for every spinal fluid), (3) bacterial contamination in spinal fluids should be avoided.

We studied the effect of the introduction of bacteria into fluids giving a positive reaction. Bacterial contamination weakens the reaction and a considerable contamination may change a positive reaction to a negative. Spinal fluids kept "bacteria-free" have given the same reaction for weeks.

In Table I a group of typical reactions is indicated by expressing the color change with numbers, ± representing the slightest increase

TABLE I.—TYPICAL REACTIONS.

Dilutions of cerebrospinal fluid	10	20	40	80	160	320	640	1280	2560	5120
Syphilis, weak		2	3	4	4	3	1	0	0	0
Syphilis, strong	1	4	5	5	5	5	5	5	3	0
Tubercular meningitis	±	±	±	±	2	4	2	0	0	0
Purulent meningitis	±	±	±	1	2	3	4	5	3	1
Negative	0	±	±	±	0	0	0	0	0	0

in blue tint, 1 a slightly greater change, and so on through 5, which represents an absolutely colorless solution. The maximum intensity of change and not the quantitative amount of change has diagnostic value. All readings were made in one hour and confirmed the next day.

In Table II the cases are grouped together with routine laboratory examinations of blood and spinal fluids and clinical diagnoses. We have taken 100 consecutive cases with 122 tests and have compared the results obtained by the gold reaction with the clinical diagnoses and other "laboratory tests."

In Group I, clinically diagnosed as Tabes, the gold reaction agreed with the clinical diagnosis in every case. In 9 of these cases the blood and spinal fluid were negative to the Wassermann reaction. In two cases all other laboratory data listed were negative; the patients had an acknowledged syphilitic history and the clinical evidences of tabes. In a second case the other data were negative except for the increased cell count.

In Group II, clinically general paresis, a positive gold reaction for syphilis was obtained in all cases with one exception, which was an early general paresis. In this case the other laboratory findings listed were also negative, clinical examination being the sole basis for diagnosis. The Wassermann reaction was particularly effective in this group.

Group III, cerebrospinal syphilis, is not noteworthy except in the relative intensity of the resulting gold reaction. Half of these cases show a strong reaction, being in this respect comparable with those of general paresis and greatly exceeding those of tabes, which only showed 25 per cent. of strong reactions.

TABLE II.

Disease.	Cases.	Tests.	Blood. Wassermann.				Spinal fluid. Wassermann.				Spinal fluid. Cells.			Spinal fluid. Globulin.				Gold reaction.		
			+	—	±	○	+	—	±	○	5 or more.	Less than 5.	○	+	—	○	±	Typical reaction for syphilis.	Positive reaction not typical of syphilis.	No reaction.
Tabes	24	28	4	12	2	6	11	12	1	..	10	11	3	7	7	10	..	28		
General paresis	12	17	8	3	1	..	10	1	1	..	10	1	1	9	1	1	1	16	..	1
Cerebrospinal syphilis	8	10	3	3	2	..	6	..	2	..	8	..	..	7	..	1	..	10		
Cerebral syphilis	3	3	1	2	..	..	..	3	..	..	1	1	1	1	..	2	..	3		
Spinal syphilis	4	5	3	..	1	..	3	1	..	..	3	..	1	3	..	1	..	4	..	1
Mental diseases	8	8	2	6	..	..	1	7	..	..	..	4	4	..	3	5	..	3	..	5
Tuberculous meningitis	4	5	1	1	2	..	..	..	1	3	4	..	..	4	..	..	..	..	5	
Purulent meningitis	1	4	..	..	1	..	..	..	..	1	1	..	..	1	..	..	..	..	4	
Epidemic cerebrospinal meningitis	1	2	..	..	1	..	..	..	..	1	1	..	..	1	..	..	..	..	2	
Influenzal meningitis	1	1	..	..	1	..	..	..	..	1	1	..	..	1	..	..	..	..	1	
Brain tumor	2	2	..	2	..	..	..	2	..	..	..	..	2	1	..	1	..	..	1	1
Poliomyelitis	1	2	..	1	..	..	..	1	..	..	..	1	..	..	..	1	..	..	..	2
Epilepsy	1	1	1	..	..	..	..	1	..	..	..	..	1	..	..	1	..	..	..	1
Miscellaneous diseases	15	15	..	15	..	..	..	1	..	..	2	10	3	1	7	7	..	..	..	15
Syphilis, but not of the central nervous system	8	9	4	1	3	..	..	8	..	..	2	5	1	..	4	4	..	4	..	5
Cases giving conflicting reaction	7	10	..	5	2	..	..	7	..	..	..	..	7	1	3	3	..	7	..	3

+ = positive. — = Negative. ± = Doubtful. ○ = Data not obtained.

Group IV, cerebral lues, presents one interesting case which was clinically diagnosed as polioencephalitis, and which later showed a typical gold reaction for syphilis. A syphilitic etiology was confirmed by a positive blood in spite of a negative spinal fluid to the Wassermann reaction. The patient died two weeks after the test, but there was no autopsy. A second case was negative to the Wassermann reaction in spinal fluid and blood, and the cell count was not increased, and there was no record of the globulin content. The gold test was positive.

Group V, spinal syphilis, contains a case of gumma of the cord in which all laboratory data except increased globulin content were negative. The gold reaction was also negative. This case improved under salvarsan. A second case was negative to the gold upon first examination, but later showed a positive result on another spinal fluid, the case being clinically syphilis, with a previous positive Wassermann reaction.

Group VI, which includes dementia precox, manic-depressive insanity, delirium tremens, alcoholic delusions, and a moral defective, shows the following analysis: One case of manic-depressive insanity with a positive Wassermann reaction on the blood had a gold test positive for syphilis. This latter result is not, however, absolutely trustworthy because of a slight blood tinge in the specimen of spinal fluid examined. Another case with a positive Wassermann blood and spinal fluid in a moral defective gave a positive gold test. A third case of questionable dementia precox in a woman, aged thirty-seven years, in which all the evidence was negative except that the spinal fluid was obtained under increased pressure, gave a positive reaction to the gold test. We have noted a number of cases clinically dementia precox which gave a positive Wassermann reaction in blood and spinal fluid or both.

Groups VII, VIII, IX, and X include the cases of meningitis. In the gold test all gave the changes of color in the high dilutions of the gold solution. (See Table I.) These reactions are easily differentiated from the reactions in the lower dilutions that are typical of syphilis.

Group XI. Two cases clinically brain tumor, one negative to the gold, but not typical of syphilis. The positive reaction in this case is similar to the reaction of tubercular meningitis.

Group XII. The one case of poliomyelitis on which two tests were done, gave negative gold reactions.

Group XIII. A case of epilepsy with other negative findings except a moderately positive Wassermann reaction on the blood, gave a negative gold reaction.

Group XIV consists of acute and chronic disease in which syphilis could be excluded with clinical certainty and gave a negative gold reaction in each case. This group includes one case of cerebral hemorrhage.

Group XV includes cases of syphilis, but with no evidence of any lesion in the central nervous system. The gold test was positive in four tests on three cases, all of which had positive Wassermann reactions in the blood.

The last group is summarized briefly as follows:

A case of cancer of the intestine which gave a positive and a negative gold reaction on the same fluid. The tests, however, were at intervals of over a week and the resulting bacterial contamination would easily account for this difference.

A case of gastric ulcer, with the same type of reaction as above, in which autopsy revealed gastric ulcer. The history was suspicious of syphilis, and the autopsy being a restricted one, gave no opportunity for examination of the spinal cord.

A case of acute pancreatitis, tested in our earlier experience with the reaction, gave a somewhat doubtful change.

A case of arteriosclerosis, with other negative findings for syphilis, gave a positive gold for this disease.

A case of pernicious anemia with nerve symptoms, which had been given salvarsan, showed a positive gold reaction for syphilis.

A doubtful case in a boy, aged four years, in whom either tubercular meningitis, poliomyelitis, or acute gastro-enteritis with cerebral symptoms was suspected, gave a positive reaction for syphilis on repetition.

A case with cancer of the stomach gave a positive and negative reaction under the same conditions as the second case. Autopsy revealed cancer of the stomach. The central nervous system was not examined.

In our experience the cases with syphilitic etiology do not give reactions typical for the resulting disease. For instance, it is not possible to differentiate between tabes, general paresis, and cerebrospinal syphilis, etc., except as above noted, that the reaction is more likely to be strong in general paresis and cerebrospinal syphilis.

Just how the reaction takes place and to what protein it is due is not known, and our study throws no light upon the question.

Discussion and Summary.—Scrutiny of the tables shows that the gold reaction is not parallel with the blood Wassermann reaction, the spinal fluid Wassermann reaction, the globulin or the cell count, but apparently more constant in syphilitic affections than any of the other tests.

The blood Wassermann reaction is present in only 43 per cent. of the cases diagnosed as syphilis of the central nervous system.

The Wassermann reaction on the cerebrospinal fluid was positive in 59 per cent. of the cases. Both were absent in 24 per cent. of the cases of presumable syphilis of the central nervous system. It is obvious then that it is not possible to exclude syphilis of the central nervous system on the basis of the Wassermann reaction on the blood or cerebrospinal fluid, or both.

Cell counts above 10 were found in 63 per cent. of the cases of syphilis of the central nervous system, and the counts were below 10 in 27 per cent. of the cases diagnosed as syphilis of the central nervous system. Cell counts under 5 are certainly within normal limits. Counts of 5 to 10 are doubtful. Counts above 5 were present in 75 per cent. of the cases. However, the cell counts are found in other conditions than syphilis beside purulent meningitis, notably tubercular and influenzal meningitis, anterior poliomyelitis, and brain tumor. One of us (Lee) has observed a cell count of 53 shortly after a uremic convulsion, in which case two days later the count was 0. The other tests were negative. The colloidal gold test was not done in this case. The cell counts are of distinct value, as an abnormal count is found in a high percentage of cases of syphilitic affection of the central nervous system. The value of cell counts is somewhat impaired by the fact that other conditions which may be confused clinically with syphilis often show a great increase in the number of cells.

The globulin test (Noguchi's[6] butyric acid test and Nonne's[7] ammonium sulphate test) has not been satisfactory in our hands. A standard of positive and negative reactions is difficult and ill-defined. There were many doubtful reactions.

The globulin test was positive in 77 per cent. of tested cases of syphilis of the central nervous system. This test is also positive in cases of tubercular meningitis, brain tumor, and other conditions.

The gold reaction typical of syphilis has occurred only twice in the absence of blood Wassermann reaction, spinal fluid Wassemann reaction, cell counts, and globulin. In both these cases the gold reactions were confirmed by the clincal diagnosis. The gold reaction usually occurs in combination with one of the other tests, but there is no constant association with any test. A gold reaction typical for syphilis has been obtained in the absence of each of the other tests. A negative gold reaction was obtained in only two cases in which the condition of the central nervous system was diagnosed as syphilitic.

The diagnosis of these cases is often difficult, and is occasionally determined by the laboratory findings. We have accepted the clinical diagnosis as final.

The disadvantages of the test are that the presence of blood or serum vitiates the findings, and that a certain amount of care must be used to prevent extraneous protein substances from contaminating the fluid or the reagent.

The advantages of the test are the small amount of cerebrospinal fluid required, 0.2 c.c., its technical simplicity, the sharpness of the reaction, and its delicacy.

[6] Serum Diagnosis of Syphilis (2d edition), p. 155.

[7] Syphilis and the Nervous System (translated by G. Ball), p. 341.

CONCLUSIONS. A gold reaction typical for syphilis is nearly constant in cases of syphilis of the central nervous system.

This test is more delicate than the blood Wassermann reaction, spinal fluid Wassermann reaction, cell count, and globulin content.

The test has the advantage that it gives a reaction with pathological spinal fluids due to other causes than syphilis, that is characteristic and easily differentiated from the reaction typical for syphilis.

Our experience confirms the findings of other observers that the gold test is delicate, and that the margin of error is exceedingly small.

THE EFFECT OF EXTRACTS OF SHEEPS' THYROID AND OF PATHOLOGICAL HUMAN THYROID UPON THE FATIGUE CURVE OF VOLUNTARY MUSCLE

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MUSCULAR weakness, independent of the emaciation which develops sooner or later as a feature of Graves' disease, is a symptom which has impressed many observers of this condition. Dock[1] in his article upon exophthalmic goitre in Osler and McCrae's *Modern Medicine* discusses this feature as follows: "Muscular weakness is another characteristic symptom. It is so rarely absent that it is strange that Askanazy's finding of muscular atrophy and degeneration has not been more widely confirmed. Fr. Müller gives some characteristic measurements showing the degree of weakness."

	Basedow's disease. Kilograms.		Normal woman. Kilograms.	
	R.	L.	R.	L.
Shoulder, adduction	3.8	3.6	13	12
Shoulder, abduction	1.9	1.5	15	12
Elbow, flexion	4.8	4.0	30	25
Elbow, extension	5.6	4.8	18	14
Finger, flexion	6.5	5.5	20	18
Hip-joint flexion	4.6	4.1	30	
Hip-joint extension	5.1	4.6	35	
Hip-joint adduction	4.5	4.5	15	
Hip-joint abduction	4.0	4.0	15	
Knee flexion	7.1	6.6	30	
Knee extension	13.4	12.1	40	

As a further development of the same line of observation, a definite muscular syndrome, that of myasthenia gravis, is not

[1] Exophthalmic Goitre, Osler and McCrae, 1909, vol. vi.

infrequently associated with exophthalmic goitre. Since 1877, when Wilkes reported the first case of myasthenia gravis, we find 197 recorded cases. In these reports there are 8 cases of pronounced combination of the two conditions.[2] If this were all we should still be within the realm of coincidence, but the facts that comparatively few nervous diseases, with the exception of hysteria, chorea, and paralysis agitans, complicate exophthalmic goitre and that many clinicians (Oppenheim, Kalischer, Goldflam, Finizio, Karplus, Murri, Warner, Bristowe, Ballet, Finlayson, Liebrecht, Rothmann, Marina, Camuset, Suckling and others) have observed some of the symptoms of Graves' disease in profound cases of myasthenia gravis, and *vice versa*, lead us rather forcibly to the idea of a closer connection. We can, therefore, as Goldflam expresses it, "accept a certain relation between the two diseases, because the combination of asthenic palsy with prominent or mild symptoms of Basedow's disease occurs so often, rather than speak of a mere coincidence of occurrence. This is also the opinion of Oppenheim."[3]

Experiments with thyroid feeding have been most unsatisfactory in regard to producing a definite picture of exophthalmic goitre, but weakness—not certainly dependent upon loss of weight—has appeared. Unfortunately, this symptom has not been specially considered in endeavors to produce hyperthyroidism in animals, which too often have been taken up with attempts to estimate less measurable and controllable criteria, such as nervousness, exophthalmos, tachycardia, etc. Opinions are united upon the harm done by administering thyroid in pronounced cases of Graves' disease, and we find no well-watched cases of myasthenia in which thyroid has been helpful, whereas there are several in which it has seemed to augment the condition—a fact necessitating prompt withdrawal. Added to this, Rennie[4] reports a rapidly fatal case of myasthenia gravis in a jockey who had been taking large quantities of thyroid to reduce his weight, but who presented no evidence of exophthalmic goitre.

Mosse[5] administered thyroid material to two hospital patients who had been taught to use the ergograph, and believed he secured evidence leading to the conclusion that their muscular power was increased. His experiments are few and his results not beyond the possibilities of error with this apparatus. Markeloff[6] injected glycerin extracts of thyroid into dogs and found a slight degree of resistance to fatigue. He believes thyroid markedly increases the irritability of the neuromuscular apparatus. His dosage of

[2] Arch. f. Psychiat., 1886, xvii, Heft 2 (Jendrassik); Berlin. klin. Woch., 1899, xxxvi, p. 574 (Remak); Arch. de Neurol., 1905, xix (Brissaud and Bauer); Zeitsch. f. Augenheilk., 1904, xii (Loeser, 2 cases); Neurolog. Centralbl., 1904, vol. xxiii (Meyerstein); Rev. Neurol. and Psych., 1908, vi (Rennie); ibid., 1913, vol. xi (Rennie).

[3] Goldflam, Neurolog. Centralbl., 1902, vol. xxi, p. 305.

[4] Australasian Med. Gaz., May, 1904.

[5] Arch. de Physiol., 1898, vol. x.

[6] Obos. Psik. Neurol., etc., St. Petersburg, 1912, vol. xvii.

thyroid in view of Carlson's[7] observations upon the resistance of dogs to thyroid material would seem to be extremely small, and if a positive effect can be obtained by such light administration it is most remarkable. Ioteyko[8] made Ringer's solution extracts of Merck's dried sheep thyroid, which correspond in strength to the 2 per cent. solutions used by ourselves. Immersion of frogs' muscles in such solutions gave evidence of stimulation. Similar experiments using Armour's thyroid gave no results in our hands.

EXPERIMENTAL WORK.—In view of such incomplete testimony as to the action of commercial thyroid material upon muscle, it became necessary to make some experiments with it before attempting to use material recognized as being abnormal. For this purpose the desiccated sheeps' thyroid prepared by Armour & Co. was selected. It is said to contain 0.2 per cent. of iodine. A weighed quantity of this powder was macerated in Ringer's solution isotonic for the frog.[9] This maceration was carried on in the ice-chest over-night, and in the morning the filtrate contained the substance used in the experiments. By such a method only a small amount of the original material is represented in the filtrate, as the dried gland is but slightly soluble. For purposes of convenience, however, we term filtrations which resulted from the use of 5 grams of dried thyroid per 100 c.c. of Ringer's solution, 5 per cent. solutions; those which before filtration contained 1 gram, 1 per cent. solutions, and so on throughout the entire series. A 3 per cent. solution is straw-colored, clear, slightly viscid, and faintly acid to litmus. Experiments have been made at room temperature and at all seasons. Frogs have been the test animals. Different varieties gave identical results. Direct stimulation has been used throughout.

TECHNIQUE.—A cannula was inserted into the right branch of the truncus arteriosus, the left being tied and the sinus venosus opened. When the perfusion was ready to start, one leg was amputated at the thigh and the stump tightly ligatured. The perfusing fluid was turned on and allowed to run for ten minutes. By this method the head is not perfused but the abdominal vessels remain in the circuit; 4 to 5 cm. a minute was the rate employed, maintained evenly by a burette constructed upon the Mariotte principle.

Both legs are thus deprived of the normal circulation at the same time. The leg first amputated lies for ten minutes bathed in its own lymph, the other is perfused with the test solution. The two gastrocnemii are placed in separate muscle chambers, but in the same electrical circuit and record simultaneously. Maximal single break shocks at the rate of thirty-four per minute have been used, Edison and Laland cells being the source of the current.

[7] Amer. Jour. Phys., 1912, vol. xxx. [8] Jour. Med. de Bruxelles, 1903, Nos. 27 and 29.

[9] Sodium chloride, 0.7 per cent.; potassium chloride, 0.03 per cent.; calcium chloride, 0.026 per cent.

With such preparations one may make the ordinary fatigue curves upon a slowly moving drum or superimposed curves, in this last case recording every seventy-fifth contraction.

By this technique a number of tracings were made, using Ringer's solution alone. There was no evidence of depression. The muscles made identical curves or else the perfused one performed a small amount more work.

Tracing 1 shows the effect of 3 per cent. thyroid. There is slight stimulation followed by early and marked depression. Tracing 2, the superimposed curve with the same solution, shows an identical result. Tracings 3 and 4 illustrate the effects of a 1 per cent. solution, which is indistinguishable from that of pure Ringer's solution. We found no result below 1 per cent., at which point there was evidence of stimulation occasionally. At no strength of solution was there evidence of distinctive effect, as, for instance, that of veratrin. The thyroid produced nothing except a simple quantitative lack of efficiency.

COMPARATIVE EXPERIMENTS WITH PATHOLOGICAL HUMAN GLANDS.—The glands used in the following experiments were taken from the operating-room in a sterile jar and minced aseptically. They were then dried in a current of air filtered through four layers of surgical gauze at a temperature from 40° to 50° C. Complete drying took a variable amount of time, but there was no odor nor evidence of gross contamination. After drying, the glands were finely powdered and then extracted with light gasoline[10] in Soxhlet extractors to render them fat-free. This process parallels that used by Armour & Co. in the preparation of sheeps' thyroid, with the exception that the sheeps' glands are collected without aseptic precautions from animals which have been thoroughly bled. After fat extraction the dried powder was placed in sterile bottles and left until used; the technique of making solutions and records was the same as we have detailed for sheeps' thyroid. As the individual glands yield small amounts of dried material, 3 per cent. solutions have been the strongest employed.

PATHOLOGICAL GLAND IV.—The patient, Mrs. R., aged twenty-one years, one year before operation noticed that her neck was swollen and immediately began to complain of tremor, tachycardia, great nervousness, and exophthalmos. These symptoms continued until April 22, 1912, when she was operated upon by Dr. G. P. Müller. Following the operation there was an explosion of hyperthyroidism, but later she progressed favorably. The case was diagnosed clinically as one of pronounced Graves' disease. Grossly the gland contained a few colloid cysts but was largely pale, meaty thyroid tissue. The microscope showed a characteristic cellularity and increase in mucoid material.

[10] Gasoline, 88°, Baumé, fractional distillation yields 65 per cent. below 60° C., and practically 100 per cent. below 100° C.

Tracing 5 shows the effect of a 3 per cent. solution of this gland. There is a large amount of depression accompanied by irregularity.

FIG. 1.—Upper muscle normal. Lower muscle 3 per cent. sheeps' thyroid. Thirty-four stimuli per minute.

FIG. 2.—Superimposed curve. Upper muscle normal. Lower muscle 3 per cent. sheeps' thyroid. Thirty-four stimuli per minute. Seventy-fifths recorded.

This irregularity was observed occasionally in our tracings made with sheeps' thyroid, but was rare. In those made with glands

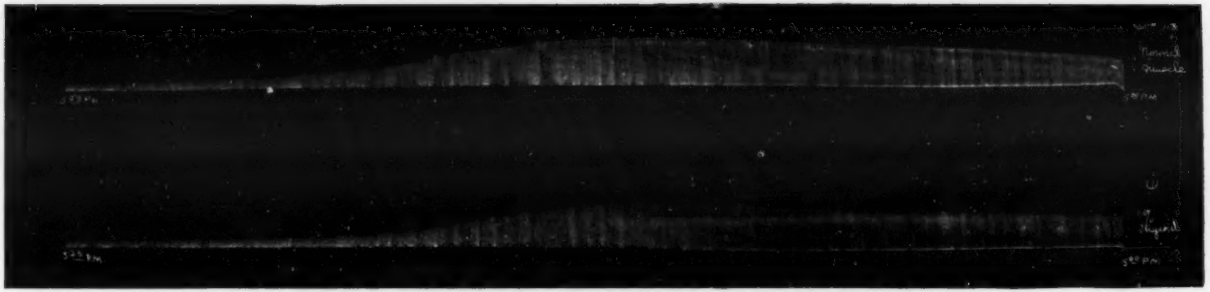

FIG. 3.—Upper muscle normal. Lower muscle 1 per cent. sheeps' thyroid. Thirty-four stimuli per minute

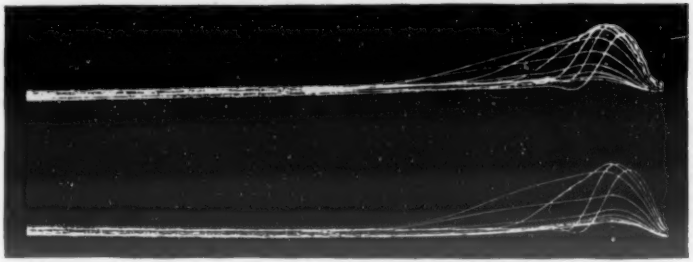

FIG 4.—Superimposed curve. Upper muscle normal. Lower muscle 1 per cent. sheeps' thyroid. Thirty-four stimuli per minute. Seventy-fifths recorded.

from cases of Graves' disease it occurred constantly. Tracing 6 demonstrates an identical result. Tracings 7 and 8 show the effects of a 1 per cent. solution. There is slight stimulation, as we sometimes found to be the case with similar strengths of sheeps' thyroid.

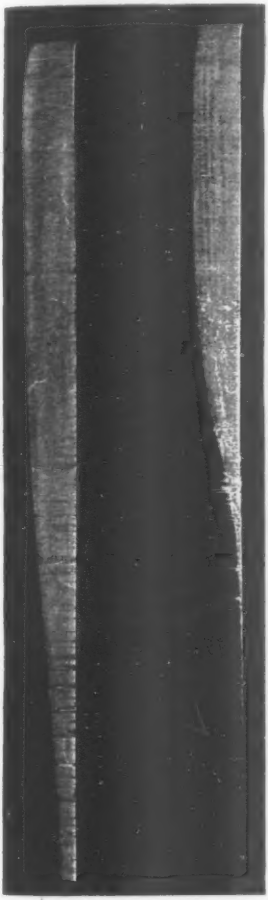

FIG. 5.—Upper muscle normal. Lower muscle 3 per cent. gland IV (pronounced Graves' disease). Thirty-four stimuli per minute.

FIG. 6.—Superimposed curve. Upper muscle normal. Lower muscle 3 per cent. gland IV (pronounced Graves' disease). Thirty-four stimuli per minute. Seventy-fifths recorded.

PATHOLOGICAL GLAND V.—The patient, Mrs. S., aged fifty-four years, had suffered from a disfiguring goitre for many years, which had been increasing rapidly in size during the two years prior to operation. At the time of operation she was able to swallow liquids alone, and had become exceedingly emaciated. There

FIG. 7.—Upper muscle normal. Lower muscle 1 per cent. gland IV (pronounced Graves' disease). Thirty-four stimuli per minute.

FIG. 8.—Superimposed curve. Upper muscle normal. Lower muscle 1 per cent. gland IV (pronounced Graves' disease). Thirty-four stimuli per minute. Seventy-fifths recorded.

were no symptoms of Graves' disease or myxedema. Dr. C. H. Frazier removed the gland, which was diagnosed pathologically as

FIG. 9.—Upper muscle normal. Lower muscle 3 per cent. gland V (colloid goitre). Thirty-four stimuli per minute.

FIG. 10.—Superimposed curve. Upper muscle normal. Lower muscle 3 per cent. gland V. Thirty-four stimuli per minute. Seventy-fifths recorded.

a colloid adenoma. It was made up entirely of large and small cysts filled with colloid material.

Tracings 9 and 10 illustrate the effect of 3 per cent. solutions. The thyroid muscle has done as much work as the normal, and the absence of irregularity is easily seen; 1 per cent. solutions were without effect.

In all we have experimented with material removed from nine thyroid cases. Of these three were pronounced colloid goitres operated upon for pressure symptoms and for disfigurement. Perfusion with 3 per cent. solutions of these glands gave no result in two cases and a slight suggestion of depression in one; 1 per cent. solutions were without effect. The tracings never showed the irregularities we have mentioned in connection with the parenchymatous goitres. Two cases were indefinite types clinically and pathologically. They occurred in girls of sixteen and seventeen, nervousness and slight enlargement of the thyroid being the chief symptoms. With one we obtained no result by 3 per cent. perfusion. In the other, which was as nearly normal human thyroid as one could obtain, we obtained depression, but of a less pronounced type than with our sheeps' thyroid or with our parenchymatous goitres. In the four remaining cases there was undoubted Graves' disease, the severity of which varied. In one there had been a tumor of the thyroid for a year. Exophthalmos and palpitation were beginning, but the patient could still work, and asked for operation mainly on account of disfigurement. Her gland after removal showed active hyperplasia, absence of colloid, and large amounts of mucinous material; 3 per cent. extracts caused marked depression, but none of the irregularity characteristic of our other cases. The other three cases were pronounced types of Graves' disease. Tracings from these glands made a most uniform picture following the type illustrating this paper. Depression and irregularity were the features.

Since the cystic colloid glands contain a large amount of material insoluble in water, it is reasonable to assume that their solutions contain a lower percentage of extractives than those of pure parenchymatous goitres. Disregarding the question as to whether or no solutions of dried gland contain the unknown active constituent of the thyroid, it is possible that our uniform effects may be due to a difference in strength of solution which the difference in solubility indicates. This matter could be controlled if we had access to large numbers of glands and could use those from which pure colloid could be obtained. It must be noted, also, that the experiments with both types of pathological glands were done during March and April. This may account for the irregular contractions we have observed in our parenchymatous gland cases. Controls with pure Ringer's solution and colloid gland solutions failed, however, to give irregularities during the same period.

CONCLUSIONS.—1. Ringer's solution extracts of dried sheeps' thyroid caused depression in 3 per cent. solutions made after our

technique. The depression gave way to slight stimulation between 1 and 2 per cent. of strength. At 1 per cent. there was usually no effect distinguishable from pure Ringers' solution.

2. Similar material from cases of Graves' disease gave an equal amount of depression. Clinical observation upon myasthenia gravis and exophthalmic goitre is suggestive in this relation. In addition there was irregularity in the strength of contractions, but the series is much too small to call this a specific attribute.

3. Extracts from cases of colloid goitre gave in most cases no depression; and in all less depression than was obtained with either the sheeps' thyroid or with extracts of parenchymatous goitres. There is no irregularity in the strength of contractions such as was noticed with the latter type.

FURTHER EXPERIENCES OF THE TREATMENT OF IMPERFECTLY DESCENDED TESTICLES.

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Some months ago I was asked by a doctor "how I treated cases of imperfectly descended testicles now," and appreciated clearly how impossible it was to give an answer sufficiently concise to be clear enough to satisfy the hearer. Going home, I communed with the records of the cases which I had done in the last ten years, *i. e.*, since I published a full account of my opinions and practice on the subject. In the number of the *British Medical Journal* for June 4, 1904, I published a paper on "The Value of the Imperfectly Descended Testicle, the Advisability and Value of the Operations Performed for its Relief." Since then a period of about ten years has elapsed, bringing much experience, which must of necessity have modified the conclusions arrived at in 1904. The advance of time has increased my interest in the subject, while the further experience has added to knowledge of the pathology of the condition and the results of treatment.

To begin, the imperfect descent of the testicle is in almost all cases a congenital malformation or deformity, due to some condition (or conditions) which, by depriving the gland of its full power of development, has arrested it in the course of its descent. The congenital malformation under consideration is practically always associated with arrested development of the tunica vaginalis, leaving, at least, a potential hernia sac. In the associated deformity the tunica vaginalis remains in communication with the peritoneal

cavity, a condition disposing to the development of a hernia, a total hernia sac.

Upon being confronted with a patient with imperfect descent of the testicle, it is often impossible to decide if the condition of imperfect descent is temporary or permanent; that is to say, is the testicle merely belated in its descent or not? Various people arrive at the same stage of development at various times. So long as no hernia is present, there need be no hurry in determining the answer to this question. Neither need there be any hurry if the malformation is only unilateral.

This expectant attitude is terminated either by:

1. The recognition of a hernia accompanying the imperfect descent, or

2. The recognition that the imperfect descent is not mere belatedness.

Either of these two occurrences terminates the period of waiting and indicates the need for active treatment, operation. As these factors are only two in number, it is well to consider how and why they indicate the termination of the period of inactivity and initiate that of activity.

Hernia. The presence of hernia in association with an imperfectly descended testicle indicates the fact that operation is necessary for its cure. Indeed, there is no other treatment for the hernia; a truss would press on the testicle or its vessels. Moreover, *the non-separation of the tunica vaginalis and peritoneum prevent the testicle from descending,* even if it were capable of doing so. The hernial sac holds the gland up. Hence the cure of the accompanying hernial sac, by nature or art, will aid the testicular anomaly to be cured. In separating the sac from the cord, great care must be exercised to avoid injury to the vessels, for such an injury is known to militate greatly against the testicle subsequently having any physiological value.

The Persistence of the Deformity. When the testicle has been imperfectly descended for sufficient time, say until the patient is seven years old, to show that the condition is a permanency and no temporary anomaly of a gland belated in its descent, it is necessary to operate. Such a proceeding may, in the main, be done in one of three ways:

1. The accompanying hernial sac may be divided and stripped of the cord, allowing the testicle to descend into the scrotum. Any but the mildest scrotal fixation is merely a prelude to failure, anatomical or physiological. Such an operation is called an orchidoplasty or an orchidopexy.

2. The gland may be removed as advocated by many. This line of treatment is especially indicated when the imperfect descent is unilateral. It is satisfactory in its after-results. The operation is an orchidectomy.

3. Especially when the condition is bilateral, the gland may be returned to the abdomen, intraperitoneally. Any internal secretion which the gland may have is retained which will aid the patient to develop sexual characters, such as hair on face, male voice, male body, energy of mind and body. Such an operation is an orchidocelioplasty.

Which of the three alternatives will be performed must to a great extent be decided by the surgeon at the operation. The great principle we do know about in these cases is that should the testicle be unable to furnish an external secretion of its own power, no amount of surgical art can make it do so; while clinical experience has shown how prone surgical art, in some form of orchidopexy, is to be followed by atrophy or fibrosis, the gland losing any power it might have possessed of developing any secretion, external or internal, that before the operation it might have been capable of doing. Hence it may be laid down that orchidopexies, except in unusual instances, rob the patient of something. Sufficient years have gone by for many workers and many patients to have proved this. As yet, surgeons have no great or extended experience of orchidoplasty. But some, myself among them, can witness that it is sometimes followed by growth and descent of the gland; most often the descent is not as great as is normal, and occasionally I have seen atrophy. But I can say that the more experienced a surgeon is with these cases the less likely he is to do an orchidoplasty in an unsuitable case, obtaining a failure. Still, as surgeons can only work with the material supplied them, it is impossible to attain a perfect success always. Imperfect success may be the greatest success that the provided material allows. In such doubtful cases an orchidocelioplasty is best. The results of this last operation are difficult to estimate. Though it has been done for about fifteen years, there is nothing much to be said except:

1. It has been urged on theoretical grounds that the returned testicles are prone to become malignant. This is not so.

2. It has been urged that in the intra-abdominal position, such common diseases as gonorrheal orchitis endanger life. This is not so.

3. Apparently the intra-abdominal position abolishes any external secretion, but preserves and encourages the internal secretion; an important point, as it is in the internal secretion above that practically the whole value of the imperfectly descended testicle lies.

It is the operation more frequently done in these cases than any other. In my own work for the last ten years the percentage has been: Orchidopexy, about 10 per cent.; orchidocelioplasty, about 50 per cent.; orchidoplasty, 40 per cent.

The great infrequency of the performance of the operation of orchidopexy is the result of an extended experience of the results

of that operation not only done by myself but also when done by others. These may be shortly generalized. The immediate result of the operation is fair. Then the testicle begins to ascend, usually until the gland is in the neighborhood of the pubic spine. Some of these organs descend again, taking upward of eighteen months to do so. Such cases are the best results of the operation, and until a few years ago I thought that the last word of criticism had been said. But further experience taught that this was not so. Atrophy of the gland may come on any time within about two years of the operation. Even if a gland is well placed by operation it may atrophy. A badly situated gland may atrophy. And the conclusion was borne in upon me that *the operation of orchidopexy more frequently fails from atrophy of the gland than by not retaining that gland in a good position.*

The treatment suggested for the condition of imperfectly descended testicles can be summed up from the point of view of the age of the patient, as the condition is a congenital one.

At birth and up to the age of about five years of age watch the case to decide if the testicle is merely late in its descent or not. If a hernia is seen to be present, operate and conclude by doing an orchidoplasty.

From seven to twenty years of age, operate if a hernia is present or not. Do either an orchidoplasty, an orchidectomy, or an orchidocoelioplasty.

Above twenty years of age, do an orchidectomy.

There is another point which further experience has taught me. In my book on the *Male Diseases of General Practice*, Oxford Medical Publications, pp. 95 to 97, the subject of the "masked imperfect descent of the testicle" is considered, I believe, for the first time. Shortly the imperfect descent of the testicle is marked if the hernia which accompanies it pushes the testicle down into the scrotum. Such a condition of imperfect descent is not recognized or recognizable until the hernia sac is fully stripped up and removed, the radical cure done. The testicle then assumes the position of imperfect descent or something near it. Since the publication of that book, in 1910, I have met many examples of this condition, and am sure that it is a great deal more frequent than I formerly supposed. Such a conclusion supports in detail Mr. Hamilton Russell's theory that every hernia depends for its cause on a congenital fault. Such a congenital fault with the tunica vaginalis is likely to be accompanied by some fault in the descent of the testicle. To put the question shortly, whenever a hernia is produced through a congenital fault, it is likely that the hernial-fault is accompanied by another in the descent of the testicle. The accompanying testicular fault may be hidden by the hernia pushing the testicle scrotumward. Thus the testicular anomaly will not be recognized until the sac of the hernia has been divided

and removed. These cases I find suitable for a scrotal orchidopexy, the operation adhesion bearing a similar relation to the testicular descent as the stick to the correct growth of the scarlet runner. This is the recognition and treatment of the condition of marked imperfect descent of the testicle.

OBSERVATIONS ON THE WASSERMANN REACTION.[1]

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It is a well-known fact that there are great variations in the technique of the Wassermann reaction as conducted by different workers at the present time. Owing to these differences in technique it is not an uncommon thing for a clinician to receive contradictory reports of the test done on the serum of the same patient by different workers.

We wish to call attention to several factors in the technique which we believe are important in securing results upon which the clinician can always rely as a basis for treatment.

Titration of Complement. Many of the negative results obtained in cases of undoubted syphilis are unquestionably due to the employment of overdoses of complement and hemolytic amboceptor. The majority of descriptions of the Wassermann technique provide for double or triple doses of these reagents. The only possible reason for such excessive doses is to make allowance for and overcome any non-specific complement fixation on the part of the patient's serum or the antigen. By the method in use by us, the amount of complement available for specific fixation is the same as that required for complete hemolysis of one dose of corpuscles in the presence of one dose of amboceptor. We therefore avoid the excess of complement or amboceptor commonly used by many workers, though at the same time we do not neglect to provide sufficient complement to overcome non-specific fixation by serum or antigen. It is well known that there is some difference in the degree of non-specific absorption of complement by different sera. Browning and McKenzie go so far as to estimate the non-

[1] Read before the Pathological Society of Philadelphia, January 22, 1914, and received for publication February, 1914.

specific anticomplementary power of each individual serum to be tested as well as that of the antigen, and allow excess of complement corresponding to the sum of these doses in each individual case in reading the reaction proper. While this laborious and time-consuming procedure is theoretically correct, yet for practical purposes it is unnecessary. The non-specific absorption of complement varies so little with different sera, that in routine clinical work these variations can be ignored, and an allowance of complement based on the estimation of non-specific complement fixation in one case usually suffices for all. For our hemolytic system, we prepare a rabbit amboceptor in the usual manner of such strength that 1 c.c. of a 1 in 2000 or 1 in 3000 dilution will hemolyze 1 c.c. of a 5 per cent. suspension of washed sheep's corpuscles in the presence of 0.1 c.c. of complement. Having obtained a serum of this strength, in the test itself 1 c.c. of the amboceptor is employed in a fixed dilution of 1 in 1000, with the amount of complement necessary to cause hemolysis of the corpuscles when combined with this dose of amboceptor. Thus we do not titrate the amboceptor each time the test is made, but we do make a preliminary titration of complement.

Table I illustrates a titration for determining the minimal hemolytic dose of complement.

TABLE I.—A Titration for Determining the Minimal Hemolytic Dose of Complement.

			Incubation one hour at 37° C.	
	Complement 1 in 10 dilution.	Amboceptor 1 in 1000 dilution.	Sheep's corpuscles 5 per cent. suspension.	Result.
I	0.2 c.c.	1 c.c.	1 c.c.	Partial hemolysis.
II	0.3 c.c.	1 c.c.	1 c.c.	Almost complete hemolysis
III	0.4 c.c.	1 c.c.	1 c.c.	Complete hemolysis.
IV	0.5 c.c.	1 c.c.	1 c.c.	Complete hemolysis.
V	0.6 c.c.	1 c.c.	1 c.c.	Complete hemolysis.

In this case the minimal hemolytic dose of complement would be 0.4 c.c. of the 1 in 10 dilution. This dose makes no allowance for non-specific fixation by antigen and the patient's serum, and would therefore be insufficient for complete hemolysis in a negative case in doing the test itself. Instead, however, of employing double this amount of complement for the test itself, in order to determine the minimal hemolytic dose plus the non-specific fixation dose of complement due to the presence of serum and antigen, we make a preliminary incubation of different amounts of complement with 0.1 c.c. of pooled inactivated non-syphilitic sera and the dose of antigen to be used in the test. After incubation for one hour, the 1 in 1000 amboceptor and sheep's corpuscles are added, the tubes again incubated for one hour, at the end of which time the amount of complement in the tube in which hemolysis is just complete is taken as the amount required for the test proper, representing as it does the minimal hemolytic dose plus the amount absorbed non-specifically

by serum and antigen. This amount of complement usually ranges from 0.1 to 0.2 c.c. higher than the hemolytic dose alone, which if not allowed for, might cause a negative reaction to be read weakly positive, as by this method close readings are made.

Table II represents a titration of complement as carried out routinely before performing the tests proper.

TABLE II.—A Titration of Complement as Carried Out Routinely before Performing the Tests Proper.

	Incubation one hour at 37° C.			Incubation 1½ hours at 37° C.		
	Patient's serum, normal.	Antigen.	Complement, 1 in 10 dil.	Amboceptor, 1 in 1000 dil.	Sheep's corpuscles, 5 % sus.	Result.
I	0.1 c.c.	0.2 c.c.	0.2 c.c.	1 c.c.	1 c.c.	No hemolysis.
II	0.1 c.c.	0.2 c.c.	0.3 c.c.	1 c.c.	1 c.c.	Partial hemolysis.
III	0.1 c.c.	0.2 c.c.	0.4 c.c.	1 c.c.	1 c.c.	Almost complete hemolysis.
IV	0.1 c.c.	0.2 c.c.	0.5 c.c.	1 c.c.	1 c.c.	Complete hemolysis.
V	0.1 c.c.	0.2 c.c.	0.6 c.c.	1 c.c.	1 c.c.	Complete hemolysis.
VI	0.1 c.c.	0.2 c.c.	0.7 c.c.	1 c.c.	1 c.c.	Complete hemolysis.

In the titration illustrated the amount of complement required along with serum and antigen is 0.5 c.c., which, therefore, is the dose to be used in the test proper. It will be noted by comparison with Table I that this amount is 0.1 c.c. greater than the hemolytic unit of the particular complement serum used.

In quantitative estimation of the strength of the Wassermann reaction, we determine the number of hemolytic units of complement absorbed by a given serum in combination with the syphilitic antigen. Some syphilitic sera are capable of absorbing more than one hemolytic unit of complement, *i. e.*, of still giving complete or partial inhibition of hemolysis when two, three, or even more hemolytic doses of complement are used in the test. When desirable, therefore, additional tubes can be prepared containing two, three, or more units of complement plus the amount always to be allowed for non-specific fixation by serum and antigen.

Table III illustrates the results in a positive case of syphilis employing tubes containing one, two, and three units of complement, the unit of complement being based on the titrations given in Tables I and II. From this result we would say that the case was strongly positive, of a degree of two units.

TABLE III.—The Results in a Positive Case of Syphilis, Employing Tubes Containing One, Two, and Three Units of Complement, Based on the Titrations Given Above.

	Incubation one hour at 37° C.			Incubation one-half hour at 37° C.		
	Serum.	Antigen.	Complement, 1 in 10 dil.	Amboceptor, 1 in 1000 dil.	Corpuscles, 5 % susp.	Result.
I	0.1 c.c.	0.2 c.c.	0.5 c.c.	1 c.c.	1 c.c.	No hemolysis.
II	0.1 c.c.	0.2 c.c.	0.9 c.c.	1 c.c.	1 c.c.	No hemolysis.
III	0.1 c.c.	0.2 c.c.	1.3 c.c.	1 c.c.	1 c.c.	Complete hemolysis.

In reporting the result of the reaction, most workers employ plus signs to indicate various percentages of inhibition of hemolysis, as 1 +, 2 +, 3 +, and 4 +, the last meaning absence of hemolysis or absorption of all the complement used. Obviously this method does not indicate the strength of the reaction beyond absorption of one hemolytic dose of complement, and takes for granted that all so-called 4 + reactions are of equal strength. The erroneous assumption that treatment fails to affect the strength of the reaction in many cases of syphilis is due largely to the fact that the sera have been repeatedly found to give complete inhibition of hemolysis by this method in spite of vigorous treatment. By testing these sera during the period of treatment with several units of complement, a gradual reduction in the number of units asorbed will usually be found, even though there remain fixation of one hemolytic dose of complement. (See Table III).

Instead of employing the plus signs, we prefer to designate the reactions as negative, weakly positive, medium positive, and strongly positive, up to one unit of complement fixation, and give the number of complement units absorbed in reactions stronger than this. We believe that this method of reporting results conveys more information, as a rule, to the clinician than the plus signs. Acknowledgements are due to Dr. John L. Laird for the principles followed in quantitative determination.

Various means have been described for measuring the percentage of hemolysis in reading the results of the Wassermann reaction. We do not believe that accurate estimation of the amount of hemolysis is of importance in the majority of cases, nor can this be done by the eye alone. Yet those who employ the plus signs base their reports upon the percentage of hemolysis as measured by the eye. For those who lay stress upon the accurate measurement of hemolysis in this connection, a method employing the Duboscq colorimeter described by one of us (Ivy)[2] may be found useful.

A common cause of disagreement in results by different workers is the employment of various substances as antigens, ranging from crude alcoholic extracts of syphilitic and normal tissues, to various synthetic products formed by complicated processes. Wassermann and his followers for a long time clung to the belief that the syphilis reaction was a true antigen-antibody reaction, between the Treponema pallidum on the one hand and a specific substance produced by it in the patient's blood on the other. They were forced to modify this position by the discovery that alcoholic extracts of normal tissues, such as guinea-pig and human heart, could likewise be employed as antigens with approximately the same results. Nevertheless, it is still held by Wassermann's followers that tissues rich in spirochetes, are superior as antigens to

[2] Jour. Amer. Med. Assoc., August 10, 1912.

non-syphilitic tissues or synthetic products, and give the most reliable results in routine clinical diagnosis. We adhere to this view as the result of the use of syphilitic liver extract in over 2200 tests, in which our results have differed in no material way from those of reliable workers. This statement is made after a trial of some cholesterinized extracts of guinea-pig heart and human heart, kindly furnished by Dr. J. A. Kolmer, who with Casselman has recently reported favorably as to their reliability somewhat to the disadvantage of the syphilitic liver extract, in a paper read before the Pennsylvania State Medical Society, September, 1913. Walker and Swift[3] also claim a higher percentage of positive results for cholesterinized extracts of normal organs than for alcoholic extracts of syphilitic liver. These extracts are made by adding cholesterin to the crude alcoholic extract of normal heart in a strength of 0.4 per cent. The cholesterinized guinea-pig heart extract was used by us along with our own antigen of alcoholic extract of syphilitic fetal liver in the routine examination of 100 cases, the cholesterinized human heart extract being employed in 33 cases. These investigations covered a period of several weeks. We may say that the differences in results with the three antigens were no more marked at the end of the period during which these comparative tests were made than at the beginning, so that they cannot be ascribed to deterioration of the extracts. Careful titration of the antigens was carried out before doing the tests, and at no time was more than one-third of the anticomplementary dose used. The comparative results with syphilitic liver extract and cholesterinized guinea-pig heart extract may be divided into four groups as follows:

1. In 22 cases the results were positive with both antigens, and showed little or no difference in the degree of reaction.

2. In 8 cases the syphilitic liver extract gave a weakly positive reaction, while the cholesterinized extract gave a stronger reaction.

3. In 36 cases both antigens gave a negative result.

4. In 34 cases the syphilitic liver extract gave a negative reaction, while the cholesterinized heart extract gave a weakly positive or medium positive result. This is naturally the most important group from the clinical stand-point, 9 of these 34 cases were treated cases of syphilis exhibiting no symptoms, showing that it is more difficult to render the serum negative to the cholesterinized extract by antisyphilitic treatment than to the syphilitic liver extract. The remaining 25 of this group were cases submitted for diagnosis or who had no signs or history of syphilis. Where one antigen reacted more strongly than the other, it was always the cholesterinized heart extract. In no case did the syphilitic liver extract give a stronger reaction than the cholesterinized extract.

In the comparative tests with the cholesterinized extract of human

[3] Jour. Exper. Med., July, 1913.

heart, of 33 cases there were 6 in the first group, *i. e.*, equally positive with the two extracts; 4 in the second group, in which the cholesterinized extract gave a distinctly stronger reaction than the syphilitic liver antigen; 16 in the third group, in which both antigens gave negative results; 7 in the fourth group, which were negative with the syphilitic antigen, but positive with the cholesterinized heart extract.

In the first series, therefore, the results with the two antigens disagreed in 42 out of 100 cases, and in the second series in 11 out of 33 cases. We see from this that the cholesterinized extracts gave apparently a more "delicate" reaction than the extract of syphilitic liver, but we also found that many weakly positive results were obtained by the former in non-syphilitic cases. This last fact alone is quite sufficient in our opinion to offset any advantage in delicacy of the reaction obtained with the use of cholesterinized extracts. We feel that just as high a percentage of positive results is obtained in known or clinically apparent syphilitics with a good syphilitic liver extract as with the cholesterinized antigens, and we do not get positive results with non-syphilitic sera. This is doubtless due in part to the use of one unit of complement and amboceptor properly standardized as described above, instead of double or triple units as employed by many workers. We must conclude that with cholesterinized antigens, weakly and medium positive, and occasionally strongly positive reactions, may be obtained in many conditions other than syphilis, and in normal persons. While our experience with the use of cholesterinized extracts is limited, and we have no criticism to make of the commendable experimental studies being carried on for the improvement of the Wassermann technique, we regard the employment of these artificial antigens for routine clinical use at the present time, instead of being an advance in serological technique, as a distinct step backward. Schamberg, Kolmer, Ringer, and Raiziss[4] report that they obtained positive Wassermann reactions using the cholesterinized antigens in over 28 per cent. of 22 cases of psoriasis, in several of which syphilis could almost certainly be excluded, thus providing evidence that weak reactions with these antigens do not necessarily mean syphilis, and that only strong reactions with them should be reported as positive. Kolmer and his associates[5] state that 10 per cent. of normal sera may yield weak positive reactions with cholesterinized extracts. If therefore the results of the reaction with these extracts cannot be relied upon in a considerable percentage of cases, we see no advantage of employing them along with syphilitic liver extract. We claim that with syphilitic liver extract, using the technique described, weakly positive reactions mean nothing else but syphilis. Even granting for a moment

[4] Jour. of Cutan. Dis., October, 1913.

[5] Arch. Int. Med., December, 1913.

that the cholesterinized antigens give a more delicate reaction and may furnish positive results occasionally in cases of syphilis that are negative to the syphilitic liver extract, it is a very much less serious error to overlook an occasional case of syphilis, than to saddle a diagnosis of the disease, with all it entails, upon a patient who does not have syphilis. Considerable harm is being done at the present time by the use of unreliable non-specific or artificial extracts, in two ways: (1) The marked discrepancies between the results of the Wassermann test and the clinical findings in many cases are causing sceptical clinicians to lose confidence in the value of the reaction, and thus they are being deprived of an important diagnostic and therapeutic aid; (2) a great many unfortunate people are being treated for syphilis who have not and who never had syphilis, as the result of weakly positive and doubtful reports by workers using these antigens.

It seems to the writers that there should be some means of coöperation of Wassermann workers for standardization and uniformity of methods, to be adhered to as long as they are justified by clinical results, with the acceptance from time to time of such advances in technique as may be approved. In this way only will the serological syphilis reaction retain the confidence that its intrinsic value merits.

THE INVOLUTION OF THE NASOPHARYNX, AND ITS CLINICAL IMPORTANCE.

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The vulnerability of the nasopharynx—that gateway of almost all human diseases—is due to three causes: man's assumption of an upright position, the growth and development of the brain, and the retrograde metamorphosis of the nose, face, and teeth of man.

Too much emphasis cannot be laid on the facts that almost all diseases are air-borne; that the particles which carry the disease pass through the air to the recipient; that this passage is made comparatively easy because of an exposed and unprotected part of the air tract; that the bacteria, whether they come from the mouth or through the nose, cling to this unprotected spot, develop here, and thus the disease begins. This unprotected spot is the nasopharynx; therefore, clinically, the care of the nasopharynx is of supreme and inestimable importance.

The reasons for our estimate of the supreme importance of the nasopharyngeal region are:

1. In many diseases, the primary symptom is found in this locality.

2. The secondary symptoms are traceable from the nasopharynx.

3. The management of the nasopharyngeal region controls the distant manifestations of the disease.

4. The individual's immunity from disease is in direct proportion to the resistant power of the nasopharynx.

5. Man is more subject to air-borne diseases than quadrupeds. The reason for this is that in quadrupeds the nasopharynx has no unprotected spot. In general, the infections of animals gain entrance through the alimentary tract or skin, whereas with men infections enter through the air tract.

Clinically, primary affections of the larynx, trachea, and lungs form an extremely small proportion of the affections of the air tract. Therefore the great bulk of infections must take place through the upper air tract. The nose is known to be extremely resistant to infections; this is fortunate, as the nose serves as the outpost and occupies a most exposed position. The oropharynx is of more importance, and to it can be ascribed a number of primary infections. But we do not find the portal of entry of the bulk of infections until we reach the nasopharynx. And we find it there because in the nasopharynx is an unprotected spot which, while it becomes a culture medium for bacteria, furnishes a gateway for the entrance of the infection into the individual.

The question naturally arises: Why does Nature, that great protector, leave this space in man unprotected? The comparative study of the evolution of vertebrates explains this. The assumption of the erect position of man has left this spot without the protection of the peristaltic tube which is found in this region in quadrupeds. The erect position brings the foramen magnum and the vertebral column from a position at the posterior aspect of the skull to a position at the inferior aspect of the skull. The base of the skull is bent to give a larger area for the convexity of the brain; and the facial bones are shortened in connection with the involution of the nose, teeth, and face, thereby bringing the hard palate back close against the vertebral column. In other words, in quadrupeds the attachment of the neck is at the back of the head, and the nose and nasopharynx form a straight tube.

The elevation of man to the erect position without disturbing the orientation of his labyrinth or eye planes would have necessitated a right-angle bend in his neck had not the attachment of his vertebral column been changed from the posterior aspect of his skull, as in quadrupeds, to the inferior aspect which it now occupies. Meanwhile, the growth of man's brain required change in the configuration of the base of his skull, namely, the spheno-basilary angle formed between the plane of the upper surface of the basilar process of the occipital bone in the posterior cranial

fossa and the plane of the superior surface of the sphenoid bone between the lesser wings in the anterior fossa of the skull measured in the median line. This angle varies, forms a straight line (0 degrees) in the opossum to an angle of 75 degrees in man.

These three changes at the base of the skull encroached upon the nasopharynx, bending it until it now forms a right angle. The angle referred to is the right angle opening forward and downward, formed by the bodies of the two upper cervical vertebræ and the basilar process. This angle is the "dead" or unprotected spot in the nasopharynx. This angular area is unprotected because of its configuration. Since the vertebral column has pushed forward and the hard palate has pushed backward the nasopharynx has lost the power which it had in quadrupeds of contracting and cleaning itself by peristaltic action. Instead of the abundant ciliated epithelium found in this vicinity in quadrupeds, in man there is only a small amount of imperfectly developed ciliated epithelium next to the choanæ.

The lack of protection in this non-collapsible cuboid space is the reason why the air tract is the most susceptible region of the body; why the upper air tract is the weakest part of the air tract; why the pharynx is the least resistant region of the upper air tract; why the nasopharynx is the part of the pharynx most liable to infection; why the first tonsillar region is the most assailable part of the nasopharynx; and why the angle in the first tonsillar region is the most vulnerable point in the first tonsillar region, and therefore in the whole body.

The epithelial lining of the nasopharynx is tall, columnar, ciliated epithelium near the nasal boundary, and stratified squamous epithelium in other parts, with a variable intermediate region of non-ciliated columnar epithelium. The walls of the nasopharynx are generously supplied with lymphoid tissue. This lymphoid tissue, which is spread over nearly the whole of the walls of the nasopharynx, is very much thickened over the central and posterior part of the vault of the nasopharynx, forming several parallel sagittal ridges, with a deep sulcus in the median line. This mass of lymphoid tissue forms the two lobes of the tonsil of Luschka, or first tonsil. The pharyngeal bursa lies between the lobes of the first tonsil.

This mass of adenoid vegetation is found in a corner formed by the bending of the posterior pharyngeal wall at the angle of the nasopharynx. Here the respiratory current is bent at right angles, necessarily forming eddies, and thus providing a place where the air current slows down, favoring the lodgement of floating particles.

The angle is the point where the momentum of the floating particles and the slowing down of the air current favor their sticking to the wall. At this place, also, the ciliated columnar epithelium continuous with the ciliated epithelium of the nose changes into

non-ciliated pavement epithelium. This epithelium, since it has lost the cleansing power of the peristaltic collapsible nasopharynx of the quadruped, has no means by which to free itself from foreign material except through the uncertain flow of mucous secretions.

The oropharynx is provided with many strong muscles which act in coördination in peristaltic contraction of the oropharyngeal tube during the act of swallowing, thus squeezing out and carrying off adherent mucus and foreign material. The upper limit of this peristaltic tube is the soft palate.

The soft palate, when contracted, forms a diaphragm between the oropharynx and nasopharynx in man. The nasopharynx lies above the soft palate and the peristaltic tube which the soft palate forms with the oropharynx, and consequently the nasopharynx cannot be cleaned by muscular contraction. The nasopharynx is therefore dependent upon its ciliated epithelium to keep it clean, and to the flow of excreted mucus to wash off foreign material from the pavement and columnar epithelium lacking in cilia.

Just in this region, at the point of the bending of the respiratory current, between where the esculator takes up its burden and where the tube conveyer commences—that is, between these two mechanisms—is located the general dump, cleaned only by a precarious flow of mucus. This general nasopharyngeal dump is at the point where the "adenoid" is located. This locality, on account of its lack of protection, serves not only as the point of entry for bacteria, but also as a culture medium, where the bacteria can develop almost without hindrance. The virulent toxins which they produce may cause disturbances at distant points.

The pharyngeal tonsil, or first tonsil, appears from its position to be mechanically the most vulnerable point in the air tract, and if in the air tract, then in the body. A mass of lymphoid tissue protects it and probably serves as a barrier to the entrance of infectious organisms. Infections of the upper air tract occur oftenest in Waldeyer's ring, and in the pharyngeal tonsil more often than in any other part of the ring.

The typical changes in the course of an acute infection through the adenoids are characteristically shown in acute rhinopharyngitis. The onset is expressed by increased secretion, congestion, and swelling of the adenoid. The reaction spreads and increases in violence according to the course of the infection.

A constant characteristic in chronic inflammation, having its origin in the upper air tract, is shown in the swelling, increased secretion, altered blood-supply of the first tonsil, and the conspicuous absence of subjective symptoms.

In the first, or Luschka tonsil, as has been previously recognized in the faucial tonsil, an infection may be localized and very active; or, again, it may be extremely insignificant locally whereas the distant effects acquire a dangerous importance.

Air-borne Infections. Diseases due to air-borne infections enter the human body in three ways: through the respiratory tract, through the skin, and through the digestive tract. The diseases entering through the nasopharynx are in the maximum both in number and in importance. As scientific observations multiply, significant additions are being made to the list of infections entering through the air tract. This list now comprises the exanthemata, and nearly all diseases due to the local or distant effects of bacterial parasites. The only exceptions are the few diseases caused solely by the entrance of the pathogenic microörganisms directly into the tissue or through the walls of the alimentary canal and genito-urinary tract.

A partial list of affections which may be acquired by means of the inspired air, and many of which are exclusively thus acquired are: the exanthemata; tuberculosis; leprosy; glanders; actinomycoses; syphilis; influenza; infection by pyogenic bacteria affecting brain, cord, ears, nose, and throat, larynx or lungs, and heart; epidemic parotiditis; epidemic cerebrospinal meningitis; epidemic poliomyelitis; rheumatism; lobar pneumonia; bronchopneumonia; coryza; chorea; gastric and duodenal ulcer; arteriosclerosis; functional irregularities of the internal secretions; myxedema, Graves' disease; Addison's disease; acromegaly; pericarditis; myocarditis; endocarditis; asthma; hay fever; lymphadenitis; typhoid fever; purpura hemorrhagica; pertussis; diphtheria; nephritis; meningitis; sinusitis; mastoiditis; appendicitis; leukemia; Hodgkin's disease. All diseases except venereal disease, animal parasites, local intestinal diseases and local skin diseases may be included in the above list of diseases entering by way of the air tract.

Conclusion. The number of these primary air-tract infections is so great, and their importance is so overwhelming, that the point of entry of the infection—the nasopharynx—is invested with a spectacularly strategic importance from an etiological and clinical point of view.

METABOLISM STUDIES IN A CASE OF MYASTHENIA GRAVIS.[1]

By Theodore Diller, M.D.,

and

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I. Introduction. In the normal individual the extent of the consumption of energy is largely dependent upon the conditions of

[1] Read in abstract before the Pittsburgh Academy of Medicine, February 10, 1914.

the muscular system. On this account we would expect to find, when muscular activity and muscular tone are depressed by a pathological condition of the muscle as seen in myasthenia gravis, some changes in the metabolic functions of the body.

II. Clinical History of Case. (By Dr. Diller.) The patient is a boy, aged sixteen years, who was first examined for Dr. Diller by Dr. George J. Wright, March 3, 1913. His chief complaints were weakness in the legs, back, and in chewing. This weakness grew much worse with use of the muscles, and he frequently stumbled and fell.

The family history is good. The father and mother and two sisters and brothers are all living and well. The boy himself developed as a hearty, rugged youth, and went to school until two months ago. As a child he had measles, chicken-pox, and smallpox. He has had no acute illness in the past five years, except an attack of tonsillitis, which occurred one year ago.

The present illness began about three months ago, with drooping of the right eyelid. On several occasions he has seen double. About two months ago he noted that he would stumble over any unevenness on the street, and was conscious that his legs were weak. At the same time he noted that his jaw muscles were weak, and that they gave out, especially in chewing anything hard. Afterward he noted that his speech would become more and more indistinct as he talked. He has had no headaches nor pains of any sort. There has been no change in his mental condition.

Examination. The patient is a tall boy, large for his age, weighing 146 pounds. His color is good. There is considerable ptosis of the right lid. The face is smoothed out and expressionless. The pupils are equal, 3½ mm., respond to light and accommodation; no nystagmus. When he makes an effort to look to the left, in the extreme movement, he sees double; but there is no apparent strabismus. The muscles of the face are all weak; the masseters are distinctly weak. He cannot pucker his lips nor make forcible movements, as in laughing. The movements of the arms and legs are all weak, as tested by resistance. The gait is distinctly weak. Dyn. right, 42; left, 34. Several times in dressing and undressing the boy tired out and was compelled to rest. The effort necessary to put on his collar was almost too much for him, and he had to call his mother to his assistance. He quickly tires upon any exertion. After reading aloud a few minutes his articulation becomes indistinct and finally unintelligible. The masseters likewise tire quickly. Indeed all muscles of the body tire readily. The tendon reflexes are all greatly reduced.

No tremors; no atrophies; no sensory changes of any sort. The boy's mind seems perfectly clear.

The boy remained in the hospital about four weeks. After

the conclusion of the experiments made by Dr. Rosenbloom, covering eight days, the boy was given regularly 10 grams calcium lactate; he continues to take this remedy up to the present time (May 15.) He left the hospital after a month's stay, appearing to have made some slight improvement.

April 30, the boy's mother writes: "He does not seem any worse; in fact, I think he seems to be improving slowly. He can swallow better. He is as happy as a lark, and planning what he is going to do when he gets well."

Case of myasthenia gravis. Note general appearance of muscular weakness, especially smoothed-out appearance of face and partial ptosis of right lid. (Kindness of Dr. A. Henrici.)

III. Metabolism Study (By Dr. Rosenbloom). 1. *Review of Literature.* Pemberton[2] found a marked loss of calcium by the tissues, during a time of nitrogen retention, in a study of a case of myasthenia gravis. He also found that the creatinin excretion was lower than normal, and thinks that myasthenia gravis is a disease of deranged muscular metabolism.

Spriggs[3] also found a lessened excretion of creatinin in a case of myasthenia gravis. The uric acid excretion in his case during a period of no fever was normal.

Kaufmann[4] has studied the effect of muscular work in a case of myasthenia gravis. In the first series the patient had an intake

[2] Amer. Jour. Med. Sci., 1910, cxxxix, 816.
[3] Quart. Jour. Med., 1907, vii, 63.
[4] Monats. f. Psych. u. Neurol., 1906, xx, 299.

of 0.24 gram nitrogen and 42.4 calories per kilo body weight. During a period in which the symptoms were slight the patient retained 3.57 grams nitrogen per day; in a period when the patient daily walked about 1000 meters, typical signs of disease appeared and the nitrogen retention amounted to 2.38 grams nitrogen. In the later period, when the condition had practically disappeared, the nitrogen retention amounted to about 4.3 grams per day. When the investigations were repeated and during the first period the patient was supplied with 0.29 grams nitrogen and 48.7 calories per kilo; 4.69 grams nitrogen were retained each day.

In the second period, during which general prostration and ptosis appeared after muscular work, there was a retention of 2.26 grams nitrogen; in the third, during perfectly good health, 5.52 grams. In a third series of observation the intake was only 0.14 grams nitrogen and 4.4 calories per kilo. During the first period there was a loss of 0.28 grams nitrogen, in the second 0.96 grams, and in the third a retention of 2.55 grams daily. The relation between the total nitrogen, urea, and ammonia was as follows: In the days when the patient was well the urea was from 82 to 86 per cent. of the total nitrogen; ammonia-nitrogen, 3.5 to 3.7 per cent. When signs of fatigue appeared the urea was diminished to 62.4 to 74 per cent. of total nitrogen and the ammonia increased to 8.6 to 13.2 per cent. of the total nitrogen.

The high ammonia indicates an increased excretion of acids. He found large quantities of lactic acid in the urine and blood serum on the days of work. In this case, as in the cases of Mohr[5] and Boldt,[6] the liver was diseased, and it seemed as if the appearance of the myasthenia coincided with the extent of the formation of the intermediary products of metabolism. Kaufmann also estimated the creatinin on two days, finding it very low, but his results cannot be considered accurate, as the zinc chloride method was used. Spriggs could not detect any increase of lactic acid in the blood in the case of myasthenia gravis studied.

From the work of Loeb and others we know that the calcium ion plays an important part in normal muscular action, and on account of this fact, and the finding of Pemberton of a marked loss of calcium in a case of myasthenia gravis, we paid special attention to the calcium metabolism of our patient.

Folin has suggested that the creatinin output on a meat-free diet in any individual is a constant, independent of muscular work, and is an expression of the endogenous cellular metabolism. Shaffer believes the urinary creatinin is the result of some special process of normal metabolism, which takes place to a large extent, if not entirely, in the muscles, and that the amount of creatinin

[5] Berl. klin. Woch., 1903, No. 46.
[6] Monats. f. Psych. u. Neurol., 1906, xx, 39.

in the urine, expressed in milligrams per kilo of body weight, is an index of this special process, and claims that the muscular efficiency of the individual depends upon the intensity of this process. He found that normal individuals excreted between 7 to 11 milligrams of creatinin-nitrogen per kilogram of body weight. Spriggs believes urinary creatinin is a product of the internal structural metabolism of muscle and not of its contraction. On account of the interest in the creatinin excretion of individuals suffering from muscular disease, we also included in our study the excretion of creatinin and creatin by our patient.

2. *Metabolism Methods.* During the entire experiment upon our patient he received daily the Folin[7] diet, consisting of:

Whole milk	500 c.c.
Cream	300 c.c.
Eggs (whole)	450 gm.
Horlick's malted milk	200 gm.
Sugar	20 gm.
Salt	6 gm.
Distilled water (about)	2000 c.c.

From the fourth to eighth day of the metabolism experiment about 300 grams of egg-yolk was added to the above diet, hoping that if this patient was losing calcium the increased phosphorus intake might cause a retention of calcium. The mixture was prepared fresh every day, and portions taken out for analysis. The ammonia, total nitrogen, urea, creatin, and creatinin were estimated in the fresh urine, but the other constitutents were estimated at the end of the experiment. The feces were marked off by means of carmine into periods of two days.

(*a*) *Methods Used in Urine Analysis.* The nitrogen was estimated by the Kjeldahl method. The ammonia by the Folin[8] method. The total sulphur by the Benedict[9] method. Total and ethereal sulphates by the Folin[10] method. The inorganic sulphates computed by subtracting the ethereal sulphates from the total sulphates and the neutral sulphur by subtracting the total sulphate-sulphur from the total sulphur. Urea was estimated by the Benedict[11] method. Total phosphorus by the Neumann[12] method, weighing the phosphorus as magnesium pyrophosphate. Creatinin and creatin by the Folin[13] method. Uric acid by the Krüger-Schmidt[14] method. Calcium and magnesium by the McCrudden[15] method.

[7] Amer. Jour. Phys., 1905, xiii, 45.
[8] Zeit. f. physiol. Chem., 1902, xxxvii, 161; Amer. Jour. Phys., 1903, viii, 330.
[9] Jour. Biol. Chem., 1909, vi, 363.
[10] Amer. Jour. Phys., 1905, xiii, 51; Jour. Biol. Chem., 1906, 1, 131.
[11] Jour. Biol. Chem., 1911, viii, 405.
[12] Zeit. f. physiol. Chem., 1902, xxxvii, 129; 1904, xliii, 35.
[13] Amer. Jour. Phys., 1905, xiii, 45.
[14] Zeit. f. physiol. Chem., 1905, xlv, 1; Jour. Biol. Chem., 1908, vii, 27.
[15] Jour. Biol. Chem., 1911, x, 187.

(*b*) *Methods Used in Analysis of Food.* Nitrogen by the Kjeldahl method. Total sulphur by the Wolff and Osterberg[16] method, a modification of the Benedict method. Calcium and magnesium by the McCrudden method after ashing and extracting the ash with hydrochloric acid. Phosphorus by the Neumann method. Fat was estimated in two-day periods by extraction in Soxhlet apparatus.

(*c*) *Methods Used in Analysis of Feces.* Nitrogen by the Kjeldahl method. Sulphur by oxidizing with fuming nitric acid followed by the Benedict method. Phosphorus, calcium, and magnesium were estimated by the same methods as used for the food. Fat by the Kumagawa and Suto method.[17]

Discussion of Table I. It is of great advantage to use the Folin diet in metabolism experiments, as Folin in his fine investigations on the composition of normal urines has given us the means whereby we can compare the results obtained in diseased states, with his normal values, thereby facilitating the explanation of pathological findings. This diet is a purin-free diet, consisting of about 119 grams protein, 148 grams fat, and 225 grams carbohydrate.

It may be noted that in the last six days of the experiment the patient lost 3.6 grams nitrogen. The relation of the urea-nitrogen and ammonia-nitrogen to the total nitrogen is normal in character, showing no acidosis was present. The creatinin excretion is definitely less than normal, while the creatinin-coefficient is just about one-half the normal. This finding seems to point to the fact that myasthenia gravis may be a disease of deranged muscular metabolism.

The uric acid excretion both in amount and in relation to the total nitrogen is below normal. The amount of undetermined nitrogen excreted in the urine is normal. The protein absorption as deduced from the amount of nitrogen in the feces was also normal.

In this case of myasthenia gravis there is no doubt that the true cellular or "endogenous" metabolism is not proceeding along normal lines, as both the uric acid and creatinin excretion are much lower than normal, two constituents of urine, which form a good criterion as to the extent of the cellular metabolism. The finding seems to emphasize the necessity of considering myasthenia gravis as a disease of deranged muscular metabolism.

The accompanying tables contain the data obtained in this study:

[16] Bioch. Zeit., 1910, xxix, 429.

[17] Ibid., 1908, ix, 337.

TABLE I.—The Nitrogen Metabolism and Urinary Nitrogen Partition.

Date, 1913.	Urine.[18]														Feces			
	Volume, c.c.	Total nitrogen, grams.	Urea-nitrogen.		Ammonia.			Creatinin[19]			Uric acid.			Undetermined nitrogen.		Nitrogen.			
			Grams.	Total nitrogen, per cent.	Grams.	Nitrogen.	Grams. nitrogen. per cent.	Grams.	Nitrogen.	Total nitrogen, per cent.	Grams.	Nitrogen.	Total nitrogen, per cent.	Grams.	Total nitrogen, per cent.	Nitrogen, grams.	Nitrogen intake, per cent.	Nitrogen intake, grams.	Nitrogen balance, grams.
March 14	920	16.5	13.7	83.0	0.76	0.63	3.8	1.14	0.42	2.5	0.48	0.16	0.98	1.60	9.7	....	....	14.9	....
March 15	1070	16.5	13.7	82.8	1.21	0.99	6.0	0.81	0.30	1.8	0.46	0.15	0.91	1.36	8.3	....	....	15.6	....
March 16	2000	16.8	14.1	84.0	0.92	0.76	4.5	1.24	0.46	2.7	0.45	0.15	0.89	1.33	7.9	2.1	13.6	15.4	−3.50
March 17	1380	17.2	14.4	83.6	0.86	0.71	4.1	1.46	0.54	3.1	0.49	0.16	0.93	1.39	8.1	2.1	10.2	20.6	+1.30
March 18	1140	17.0	14.3	84.2	0.85	0.70	4.1	1.21	0.45	2.7	0.43	0.14	0.83	1.41	8.3	2.8	13.8	20.2	+0.40
March 19	2140	17.3	14.7	85.1	0.68	0.56	3.3	0.96	0.36	2.1	0.39	0.13	0.75	1.55	8.9	2.8	13.8	19.8	−0.30
March 20	1650	16.9	14.2	83.8	0.71	0.59	3.5	1.33	0.49	2.9	0.37	0.12	0.71	1.50	8.8	3.1	13.4	23.1	+3.10
March 21	1900	17.0	14.4	84.5	0.87	0.72	4.2	0.96	0.36	2.1	0.42	0.14	0.82	1.38	8.1	2.0	12.9	15.5	−4.60

[18] No creatin was present in the urine at any time.

[19] Average creatinin coefficient, 6.3 milligrams per kilo of body weight.
Average creatinin excretion, 1.04 grams per day.
Average creatinin-nitrogen excretion, 0.42 gram, or 2.5 per cent. of the total nitrogen excretion.

TABLE II.—The Sulphur Metabolism and Urinary Sulphur Partitions.

Date, 1913.	Urine.									Feces.		
	Sulphur, grams.	Sulphate sulphur.		Ethereal-sulphate sulphur.		Inorganic sulphate sulphur.		Neutral sulphur.		Sulphur, grams.	Sulphur intake, grams.	Sulphur balance, grams.
		Grams.	Total sulphur, per cent.	Grams.	Total sulphur, per cent.	Grams.	Total sulphur, per cent.	Grams.	Total sulphur, per cent.			
March 14	1.27	1.15	90.5	0.15	11.8	1.00	78.7	0.12	9.4	....	1.6	
March 15	1.30	1.16	89.2	0.20	15.4	0.96	73.8	0.14	10.8	....	1.6	
March 16	1.52	1.40	92.1	0.19	12.5	1.21	79.6	0.12	7.8	0.38	2.2	+0.30
March 17	1.36	1.30	95.6	0.10	7.3	1.20	88.3	0.06	4.4	0.38	2.2	+0.46
March 18	2.12	1.98	93.4	0.35	16.5	1.63	76.9	0.14	6.6	0.42	2.0	−0.54
March 19	2.08	2.00	96.1	0.18	8.6	1.82	87.5	0.08	3.8	0.42	2.0	−0.50
March 20	1.87	1.72	91.9	0.12	6.4	1.20	85.5	0.15	8.0	0.45	2.1	−0.12
March 21	1.45	1.30	89.6	0.15	10.3	1.15	79.3	0.15	10.1	0.45	2.0	+0.10

TABLE III.—The Calcium, Magnesium, and Phosphorous Metabolism.

Date.	Urine.			Feces.			Intake.			Balance.		
	Phosphorous, grams.	Calcium oxide, grams.	Magnesium oxide, grams.	Phosphorous, grams.	Calcium oxide, grams.	Magnesium oxide, grams.	Phosphorous, grams.	Calcium oxide, grams.	Magnesium oxide, grams.	Phosphorus, grams.	Calcium oxide, grams.	Magnesium oxide, grams.
March 14	....	0.45	0.14	...	2.2	0.10	2.6	1.8	0.32	....	−0.85	+0.08
March 15	....	0.48	0.15	...	2.4	0.10	2.6	1.8	0.32	....	−1.08	+0.07
March 16	1.31	0.60	0.15	1.4	2.1	0.12	2.4	1.9	0.37	−0.31	−0.80	+0.10
March 17	1.62	0.91	0.16	1.4	2.3	0.12	4.8	1.9	0.37	+1.06	−1.31	+0.09
March 18	1.90	0.56	0.20	1.6	2.0	0.15	5.2	2.6	0.44	+1.70	+0.04	+0.09
March 19	1.94	0.59	0.21	1.6	2.4	0.15	5.4	2.6	0.44	+1.86	−0.39	+0.08
March 20	1.98	0.95	0.20	1.9	2.6	0.14	5.5	2.8	0.43	+1.62	−0.75	+0.09
March 21	1.92	1.16	0.19	1.9	2.8	0.14	4.5	2.8	0.43	+0.68	−1.16	+0.10
Totals	10.67	5.70	1.40	9.8	18.8	1.02	28.6	18.2	3.12	+6.61	−6.3	+0.70
Averages	1.78	0.71	0.175	1.6	2.35	0.13	3.6	2.3	0.39	+1.10	−0.8	+0.087

DISCUSSION OF TABLE II. During the last six days of the experiment the patient shows a slight loss of sulphur. The amount of sulphur excreted as ethereal sulphate and as inorganic-sulphate is normal in character. The amount of neutral sulphur excreted in relation to the total sulphur is below normal. This finding also substantiates our idea that myasthenia gravis is a disease of deranged muscular metabolism, as Folin also claims that the neutral sulphur of the urine represents a partial expression of the endogenous or cellular metabolism, in the same manner as does the creatinin and uric acid excretion. As is well known, these three constituents of the urine are the truest index to the so-called "endogenous" metabolism of an individual. In this disease, we have therefore a low "endogenous" metabolism, and if it is true that the "endogenous" metabolism initiates and directs

the processes of cell life, we have a further proof for our idea that myasthenia gravis is a disease due to some metabolic perversion. It might be possible that the lack of utilization of the calcium ion prevents the "endogenous" metabolism proceeding in a normal manner.

TABLE IV.—Calcium Oxide and Magnesium Oxide Output.

Day.	Calcium oxide in urine, per cent.	Calcium oxide in feces, per cent.	Magnesium oxide in urine, per cent.	Magnesium oxide in feces, per cent.
1	16.9	83.1	58.3	41.7
2	16.6	83.4	60.0	40.0
3	22.2	77.8	55.5	44.5
4	28.3	71.7	57.1	42.9
5	21.9	78.1	57.1	42.9
6	19.7	80.3	58.3	41.7
7	26.7	73.3	58.8	41.2
8	29.2	70.8	57.6	42.4

DISCUSSION OF TABLES III AND IV. In this case of myasthenia gravis we have found a marked loss of calcium by the tissues, 6.3 grams calcium oxide in eight days, thereby confirming the findings of Pemberton. However, during a time of phosphorus retention produced by the feeding of egg-yolk, no effect was noted on the calcium metabolism.[20]

A slight retention of magnesium was found, + 0.7 gram, during the eight days. On account of the great importance that the calcium ion plays in normal muscular action, it is tempting to think that possibly it is owing to some lack of utilization of this substance that the condition of myasthenia gravis owes its origin and that the changes we have observed in the "endogenous" or cellular metabolism in this disease may be secondary to this fact and as it has long been known that the inorganic ions are necessary for normal muscular action, as a hypothesis we might say that it is owing to some disturbance in metabolism of these substances, especially calcium, that the muscular symptoms of myasthenia gravis are due. We also know that during the work of muscle, lactic acid is produced, one of the factors in the production of fatigue of muscle. May it not be that owing to the fact that the calcium not being utilized normally, the lactic acid is not neutralized by the calcium and fatigue comes on readily, one of the characteristic features of myasthenia gravis? It must also be remembered that any perversion of calcium metabolism may give rise to symptoms in two ways, first, symptoms due to the loss of the calcium, and second, symptoms due to the excess of the other bases. A direct way to attack this problem would be to

[20] Loeb (Int. Beitr. z. Path. u. Ther. d. Ernahr., 1911, iii, 237) has also found that a phosphorus retention produced by feeding lecithin, was not accompanied by a calcium or magnesium retention.

devise some method to cause these patients to retain calcium and see if this retention had any favorable effect on the disease.[21] The distribution of oxide and magnesium oxide in the feces and urine (Table IV) may be considered normal.[22] The fat metabolism in this patient (Table V) is also normal in character. In connection with the possible influence that internal secretory organs may have on calcium metabolism, it should be remembered that many have found in myasthenia gravis some disease of the thymus.[23] It is possible that other secretory organs may exert some influence on calcium metabolism. McCrudden[24] found that improvements in the symptoms of osteomalacia, following castration, was accomplished by calcium retention, where there had been a loss before. Also, it has been found, that injections of epinephrin[25] have been of value in osteomalacia and in rickets. Carnot and Slavu[26] have shown that after injection of dogs subcutaneously with epinephrin, that ossification is much greater than in the controls. Quest[27] and also Stoltzner[28] have studied the effects of epinephrin administration in rickets in relation to the calcium metabolism. Parhan[29] has studied the influence of thyroid principle on calcium metabolism in rabbits, showing that ingestion of thyroid determined a loss of calcium from the tissues, which ran parallel to the amount of thyroid ingested.

TABLE V.—The Fat Metabolism.

Date, 1913.	Fat content of feces, grams.	Fat intake, per cent.	Fat intake, grams.	Fat balance, grams.	Fat absorbed, per cent.
March 14	..	..	..	..	..
March 15	13.5	10.0	135	+121.5	90.0
March 16	14.5	10.0	145	+130.5	90.0
March 17	19.4	10.2	198	+178.6	89.8
March 18	21.1	10.2	215	+193.9	89.8
March 19	20.3	10.1	205	+184.7	89.9
March 20	20.6	10.1	208	+187.4	89.9
March 21	22.8	9.2	210	+187.2	90.8

Basch[30] has found that thymectomized dogs in comparison with controls of the same litter, revealed lessened growth, less consistency of the bones, and a changed psychical nature, two to three

[21] I hope soon to study this problem, especially the effect of various internal secretory products on the metabolism of calcium in health and disease.

[22] For list of ratio of the urinary and fecal calcium output in normal and pathological conditions, see Towles, AMER. JOUR. MED. SCI., 1910, cxl, 100. For magnesium oxide, see Renvall, Skand. Arch. f. Physiol., 1904, xvi, 94.

[23] Mandelbaum and Celler, Jour. Exper. Med., 1908, x, 808.

[24] Amer. Jour. Physiol., 1905, xiv, 211; 1906, xvii, 211.

[25] Bossi, Centralbl. f. Gynäk., 1907, Nos. 3 and 6; 1907, xxxi, 1560; Stocker, Corr.-Bl. f. Schweiz. Aerzte, 1909, xxxix, 433.

[26] Compt.-Rend. Soc. Biol., 1910, lxviii, 832.

[27] Zeitschr. expt. Path., 1908, v, 43.

[28] Jahr. f. Kinderheilk., li, Nos. 1 and 2.

[29] Compt.-Rend., 1913, lxxii, 620.

[30] Jahr. Kinderheilk., 1906, lxiv, 285; Wein. klin. Woch., 1903, xxxi, 893; Deut. mèd. Woch., 1913, xxxix, 1456.

weeks following the thymectomy. They also showed an increased irritability of the cerebral cortex and peripheral nerves and that injections of soluble calcium salts brought the irritability back to normal. MacCallum and Voegtlin[31] and also Erdheim[32] have claimed a relation exists between the parathyroid glands and calcium metabolism.[33]

THE SERUM DIAGNOSIS OF PREGNANCY AND ITS UNDERLYING PRINCIPLES.

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In his test for pregnancy, Abderhalden has opened a field which promises perhaps more for scientific investigation and for ultimate practical usefulness than any other present-day line of study. He and his pupils have devoted a great deal of brilliant investigation to the work of animal ferments, and this test for pregnancy, introducing new laboratory methods of almost unlimited possibilities, is the result of these studies. I shall not discuss the great mass of experiments dealing with this subject the results of which have been reported by various investigators within the past two years. It is too early for a critical survey. The exacting details of the method and the principles underlying it must be more thoroughly understood by those who attempt to follow Abderhalden's work before any effort can be made to reconcile results. I shall confine myself to a discussion of these principles and to a brief consideration of the technique.[1]

All metabolic processes are in last analysis an expression of ferment activity. Each body cell is armed with ferments designed not only to protect it from foreign invasion, but which enable it to meet its requirements for energy, maintain its structural integrity, and perform its specific functions. The study of these cell ferments, overshadowing in importance everything else in physiology (and perhaps in pathology), is after all still in its infancy, for we know nothing of the exact nature of the chemical composition of ferments, and are forced to recognize them solely by the character of their work.

[31] Jour. Exper. Med., 1909, ix, 118.

[32] Frankfurt Zeitsch. f. Path., 1911, vii, 178.

[33] For review of literature regarding the influence of internal secretory organs on mineral metabolism see Bayliss and Staring, Erg. d. Physiol., v, p. 664; Vincent, Erg. d. Physiol., ix, p. 145; Internal Secretion and Ductless Glands, 1912 (Arnold); Oppenheimer, Hand. d. Biochemie, 1910, 3, part 1· Biedl, Innere Sekretion, 1913.

[1] References to the voluminous literature upon animal ferments have been omitted. This may be found in complete form in Abderhalden's Abwehrfermente des tierischen Organismus. Julius Springer, Berlin.

On first thought we should expect to find the studies of ferments simplest among the unicellular bodies. We should expect their metabolic processes to move along simpler lines and to unfold themselves more readily to view. On further consideration, however, it is seen that the metabolic processes of unicellular organisms must necessarily be more complex and more difficult of access than is the case with those organisms in whose construction many kinds of cells are concerned; for with the former, absorption and excretion run parallel, and it is extremely difficult, in fact, impossible, to study in detail their manifold metabolic processes. As we go higher in the animal scale, we find specialized groups of cells, each monopolizing certain functions and gradually losing others. Such cell groups with their special functions we recognize as organs. From this viewpoint we can regard the animal organism as a cell community, each member of which, working for the good of the whole, has its definite duties to perform.

The first attempt at formation of a cell community which we call symbiosis, is seen in that mutual coöperation between unicellular bodies. Here the cells, though separate and distinct, bind themselves together because of a common interest. A little higher up the scale and we come upon the various cell groups of multicellular bodies. When one of these groups has formed an alimentary tract, it alone, as Abderhalden points out, stands in physiological relationship to the outer world. It alone determines for the organism the nature of its absorbed foodstuffs.

The prime object of digestion is to protect the body against the invasion of foreign substances, a recognition of which fact is necessary for a proper understanding of the principles upon which Abderhalden bases his work. No foodstuffs are absorbed directly. Neither proteids, carbohydrates, nor fats undergo immediate absorption, nor can they be reduced directly to their metabolic end-products. Before it is suitable for absorption, each must be broken down to its simplest building stones. This is accomplished by means of ferments produced by the intestinal epithelium and the extrinsic glands. From the mass of amino-acids and other split products thus set free, the organism chooses such building stones as are suitable for use. What immediately follows is shrouded in some doubt. Since amino-acids could not be found in the blood, it was formerly believed that they did not circulate as such, but were united during absorption to form new albumins. Recently, however, Van Slyke and Meyer have found that amino-acids do circulate as such, and in this form are carried to the body cells.

The liver holds up and rapidly destroys any excess of these absorbed bodies. The situation of this organ, between the intestinal epithelium and the body cells, where it can scrutinize and deal with all absorbed substances, is a fortunate one; for it not only aids in

the elaboration of nutritive substances, but also serves as an important defence against foreign invasion. These building stones, perhaps loosely coupled to other substances, are taken up by the muscles and other tissues, and must undergo still further elaboration before they become integral parts of the cell.

Each variety of cell, exhibiting, as we are forced to assume, a structure peculiar to itself, must necessarily select from the materials offered it those building stones which are peculiarly suited to its needs and reject those which it cannot use. This is accomplished by means of cell ferments through digestive processes which are to a certain extent at least identical in nature with those of the alimentary tract. The blood plasma—the source from which each cell draws its building material—is for all cells the same. Consequently we should expect in each kind of cell not only its own specific ferments, but in addition, ferments which are common to all cells. In the study of this, the machinery of the cell, we shall find perhaps "the surest and most direct evidence that cell function is dependent upon cell structure." Not every split-product thus formed is ready for immediate absorption. At times it must be coupled to some other substance before a satisfactory building stone results. Then follows further coupling of all these manifold building stones until the characteristic complex cell structure is completed.

As an example of such reconstruction, "An architect is directed to construct from a given building which has served a certain specific purpose, and therefore is of special design, another building destined to entirely different uses. He must first demolish the former. From the building stones thus obtained he proceeds along entirely new lines. Many of these are ready for immediate use; others must be reshaped; while still others are wholly unfit. In exactly the same manner the animal organism deals with the complicated cell material coming to it as foodstuffs. First occurs a splitting into the simple building stones, and then beyond the intestinal wall reconstruction follows according to entirely new plans."

We are accustomed to view ferment activity in too schematic a manner. The conversion by the yeast cell of dextrose into alcohol and carbon dioxide is no doubt a much more complicated process than we ordinarily think, and is probably divided into many intermediary reactions. The meaning to the cell of each of these separate reactions will, as Abderhalden points out, constitute an interesting problem for future investigation, the solution of which will no doubt permit valuable insight into cell metabolism. The cell works step by step, liberating gradually the energy contained in its absorbed substances, and probably never at one stroke converting them to metabolic end-products.

Though every body cell conforms in structure to a certain general

ground-plan common to all, those organ cells which have taken on special functions are distinguished by certain additional peculiarities of structure. We must assume for each variety of cell this specific plan of structure, else how can we explain its specific functions? Certain cells produce specific secretions, and these secretions influence solely cells of a given kind, leaving numberless others untouched. The secretion itself, the cell which produces it, and the cell which feels its influence, must each enjoy a plan of structure peculiar to itself.

With this conception of specific cell structure, and to a certain extent specific cell metabolism, we assume not only that each variety of cell within the human organism possesses its own peculiar build, but also that to a certain extent there is a variation in a given cell between two individuals of the same species. We also recognize that this cell presents still wider variations in structure when derived from animals of different species, and so on down the scale. This demands an infinite variety of structure, while the building stones at our disposal are comparatively few. The following may be quoted to show that our assumption is entirely reasonable: With three building stones we can build six different structures; with four, twenty-four; and with twenty building stones the number of possible structures is 2,432,902,008,176,640,000.

Recent experiments indicate that while the cell albumins of a given organ differ according to the animal from which the organ comes, they at the same time present certain points of similarity. To produce this similarity it is necessary only that there recur always in each of these albumins a given group which, because of certain stereochemical arrangement offers to the specific ferment suitable point for attack. This is important when we come to consider the availability for human experiment of albumins derived from organs of the lower animals.

A striking illustration of the specific adjustment of secretions to cells of a certain structure is cited by Abderhalden in the peculiar condition known as hermaphroditimus verus. These peculiar animals possess upon one side an ovary and upon the other a testis, and exhibit upon one-half of the body male and upon the other half female types of development, each stopping sharply at the midline. We must acknowledge that the secretions from each of these glands is brought in contact with all of the cells of both sides of the body; yet each brings to full development the secondary sexual characters peculiar to itself and limits them to its own body half. The secretion from the ovary finds suitable adjustment only in those body cells of the female side, and that of the testis influences only those cells built according to the male ground-plan.

The theory of specific cell structure also finds noteworthy support in the results of transplantation experiments; for heteroplasty has

never proved successful, while tissues which are closely related will usually permit grafting. Pathology furnishes still further evidence in the fact that many poisons, such, for instance, as the tetanus toxin, will attack cells of a certain kind only—those of suitable structure—and leave all others uninjured.

The cell regulates its metabolism in finest detail, both qualitatively and quantitatively, and to accomplish this it must at all times enjoy unchanging conditions in the medium surrounding it. For a given location the composition of the plasma or lymph is always the same. Each cell takes from the plasma the same substances always, and gives to it always the same waste products, and though this fluid maintains for a given point a remarkable constancy of composition, it varies as it passes from place to place in the circulation.

Substances for which the body has use and which properly belong to the organism we call "body-like," while any substance which because of its structure and configuration fails to find adjustment in the organism is termed "body-foreign." Substances belonging to the plasma are "plasma-like," and those belonging peculiarly to the cell we call "cell-like" or "organ-like." Since the albumins of the plasma, as we have seen, must undergo reconstruction before they can become a part of the cell, though plasma-like they can only be regarded as cell-foreign. In like manner, materials belonging to a given cell while cell-like are plasma-foreign; for in the course of normal metabolism they find no opportunity for entering the plasma until through a step by step splitting at the hands of the cell they have been deprived of their specific character. A plasma-foreign substance entering the blood is equally foreign whether it come from the outside world or gain entrance to the plasma through some metabolic error on the part of the cell. The body must recognize it as foreign and deal with it accordingly, no matter what its source.

The animal organism should be regarded as a closed whole. Each organ or group of cells has its own specific duties to perform and contributes its definite part to the general metabolism. Disturb one and the whole machinery is upset. Introduce from the outside some substance which has no place in this general plan, or let some substance from within appear at a place not its own, and the organism feels the shock of foreign invasion.

Invasions by body-foreign for plasma-foreign substances are not uncommon. The bacterial infections and the malignant tumors serve as examples. Abderhalden has asked the question, "What course is open to the cells when body- or plasma-foreign substances gain entrance? Are they defenceless against these substances; or is it possible for the cells beyond the intestinal tract also to break down to harmless bodies such substances and use the building stones thus set free for their own purposes?"

In seeking an answer to this question, it was found that every body cell possesses at least some ferments similar in nature to those of the intestinal tract, and the conclusion is inevitable that these ferments play an all-important role in cell metabolism. It has been found that the body cells are able by means of a hydrolytic process to split fats into alcohol and fatty acids. Carbohydrates undergo similar degradation, glycogen being converted first into dextrin and then into maltose. This last-named is then split to dextrose. Numerous investigators have concerned themselves with inquiries regarding the presence of proteolytic or peptolytic ferments in the tissues. Abderhalden and the writer found no ferments in bovine plasma capable of splitting glycyl-l-tyrosin dl-alanyl-glycin, glycyl-dl-alanin, or diglycyl-glycin; while Abderhalden and Manwaring conducting parallel experiments with red and white cells from the same specimens of blood demonstrated the presence of such ferments. Investigators have almost without exception found peptolytic ferments in the other body cells. No such ferments are found in plasma alone, but there is no doubt that the body cells and the cells of the blood are equipped with ferments capable of digesting albumen.

The question is then asked, "Does the plasma defend itself, against foreign invasion by means of these normal cell ferments, or to meet foreign invasion does it take on new properties?" Experiment shows that the plasma on experiencing the shock of such invasion acquires new ferments—ferments which are specific in action and are directed only against this particular plasma-foreign substance. If cane sugar be added to the serum obtained from a dog, no appreciable change appears within a reasonable time. If, however, the dog first receive intravenously a solution of cane sugar and after a short time the blood be drawn, it will be found that the serum so obtained has the power of converting cane sugar into dextrose. Invertin, the ferment which splits cane sugar, appears in the blood of the dog within fifteen minutes after a solution of this carbohydrate has been injected. Experimenting with the fat tributyrin, it was found that fats also stimulate the production of ferments specific for themselves.

The source of these defensive ferments is yet a matter of conjecture. No doubt all the organs, particularly the intestinal tract, the liver, and the kidneys, play a part, and the lively interest taken by the leukocytes in every form of infection or foreign invasion suggests for them an important role. On the other hand, recent observations indicate that defensive ferments are derived each from the organ against which its activities are directed.

If these facts be true, then it is possible for us to search for plasma-foreign substances by testing the blood-serum for their respective ferments. Upon this Abderhalden bases his test for pregnancy. The placenta, while body-like, is of course plasma-

foreign. Experiment has shown that a living placenta gives off constantly, though perhaps in minute degree, its albumins to the mother circulation. The manner by which this plasma-foreign albumin gains entrance is as yet a matter of doubt. It has been suggested that the cells of the chorionic villi from time to time become dislodged and thus enter the maternal blood. In certain animals, however, the nature of the circulation precludes such an accident. Perhaps at this time of rapid cell activity a certain "overproduction" and "overflow" of a new albumin takes place. In whatever manner this invasion occurs, the mother within the first eight days of pregnancy exhibits in her serum a ferment which is capable of splitting placenta albumin and this only. The blood loses this ferment from fourteen to twenty-one days after the placenta is removed.

Were the practical application of these principles to stop here, Abderhalden's work with the defensive ferments would be of minor importance, since a blood-test for pregnancy is of no great general interest. The field is infinitely broader and richer. Invasion of the organism by body-foreign and plasma-foreign substances is an accompaniment not only of pregnancy but of many pathological states, and if the promise of this work is fulfilled, we shall be able to properly characterize these states—to recognize not only the plasma-foreign substance introduced from without, but also that introduced from within and the organ from which it comes. Through the serum diagnosis of pregnancy we are introduced to the much larger field of the serum diagnosis of organ function. We assume that when one organ becomes diseased or disturbed in function, the altered metabolism causes "unripe" or plasma-foreign albumins to enter the blood. We then test the blood-serum for the resulting specific ferments. It is tested separately against the albumins of all the organs in question, and the particular albumin digested indicates the organ which is diseased.

The opportunities thus opened for studies in physiology and pathology are almost unlimited. In this way the interrelation of the various organs may be studied: the mutual dependence of the organs of internal secretion, degenerations in muscle and nerve, bacterial infections, therapeutic and toxicologic questions, ad infinitum. "The whole realm of biology offers no more alluring task than the study of how the organism reacts when the harmony of its metabolism, regulated in finest detail, is disturbed."

Reports of work in this field and suggestions as to modification of technique are appearing in great profusion. The reports from Abderhalden's laboratory and from certain German clinics give wonderfully accurate results in pregnancy and in a variety of diseases. On the other hand, numerous investigators have shown disappointment in their results and express doubt as to the specific action of the ferments. The complexity of the method and the

many pitfalls in the technique warrant always from its adherents the reply that the test was not properly carried out. All agree that before it comes into general use the present method must be changed or simplified, and Abderhalden has recently reported interesting and promising attempts at perfecting a precipitation method which will eliminate the dialysis shells. Certain of my own results have been contradictory, but one fruitful source of error has been discovered in the faulty dialysis shells. I hope to report these studies at another time.

Abderhalden stated recently that over 600 sera in his laboratory had been tested for pregnancy with less than 1 per cent. of error, and that these errors were later shown to have been avoidable. In the same report he tells of over 400 sera from cases of Graves' disease, dementia præcox, carcinoma, sarcoma, tuberculosis, and other diseases which have been tested with startlingly direct and accurate results. Fifty carcinoma sera were diagnosed without an error. In numerous instances serum diagnosis has pointed to certain diseased organs which could not have been recognized clinically.

Notwithstanding the many adverse criticisms, one cannot but recognize that such reports coming from men like Abderhalden, Lampé, and numerous others, cannot be disregarded.

Certain interesting results will serve to illustrate the value of the method. Sera from endemic goitre and myxedema are found to digest thyroid tissue. Exophthalmic goitre serum attacks thyroid, thymus, and frequently the ovary but no other tissue. Dementia præcox serum digests always the ovary or testis and usually the cerebral cortex. It has been reported that serum from patients with miliary tuberculosis will split the tubercle bacillus, and that serum from tuberculous cows splits bovine but not human tubercle bacilli.

Paltauf's case is worthy of mention. He found that a certain malignant tumor from an old woman was not split by known carcinoma serum, but was attacked by pregnancy serum. The microscopic diagnosis proved to be malignant chorioepithelioma.

Just a word regarding the present method. If the precautions prescribed are necessary (and the limited experience of the writer assures him that they are), no one can expect today to obtain satisfactory results who has not thoroughly familiarized himself first hand with Abderhalden's discussion of principles and his elaborate rules as to technique.

Briefly, the principle of the dialysis method of serum diagnosis, the method commonly used, rests upon the fact that colloidal albumin will not diffuse through an animal membrane, while its split products, peptones, and amino-acids, will pass through. The coagulated blood-free tissue of the placenta (or organ in question) is placed in a small dialysis shell, to which is added the serum to be tested. If this serum contains defensive ferments specific

for this tissue, the latter will be digested and its split products will pass through to the distilled water outside the membrane—the dialysate—which after about sixteen hours can be tested with Ninhydrin for these bodies.[2]

Precautions are numerous and essential. Absolute asepsis in every step is demanded. The dialysis shells themselves must be standardized. They should not permit the passage of albumin, but must all be equally permeable to albumin-split products.[3] The preparation of the organ albumins, "substrata," as they are called, must be perfect. When properly prepared and coagulated they are snow-white. They must not contain even the minutest traces of blood or extractive substances. Before it is available for use, each preparation must be tested by the dialysis method for remaining traces of blood. Otherwise, results will be fallacious. All utensils must be in perfect condition both as to cleanliness and asepsis. The water used must be freshly distilled and sterile. Care must be taken to see that uneven evaporation of the different dialysates is impossible.

In applying the Ninhydrin test to the dialysates, the utmost precaution must be observed to obtain in each test identical intensity of boiling. To insure accurate observations as to the resulting color reaction, test-tubes of equal caliber and thickness of wall must be used. The blood-serum must be fresh, and should be actually, not apparently, free of cells. This work should not be done in a laboratory where other chemical or bacteriological experiments are carried out, and a special incubator should be reserved. The author of the method urges that those who undertake it familiarize themselves most carefully with its every detail, and begs that no attempt be made to change the method until we can first analyze our present errors and determine their sources.

And finally as to the part the clinician is to play in these studies. Abderhalden significantly states that physiology has done its part, that it has developed the method and its principles, and that it now remains for the clinician to determine value and scope. He emphasizes the necessity for the most careful clinical study and "follow up" of all cases tested by this method, and urges that patients be carefully classified and studied in large groups or series, rather than as individuals, as only the clinician is competent to do.

I take pleasure in acknowledging my indebtedness for the principles here discussed to the writings of Professor Abderhalden, and particularly to "Abwehrfermente des tierischen Organismus."

[2] The optical method which is less adapted to clinical work depends upon the change in optical rotary power which a mixture of peptones undergoes when subjected to further splitting.

[3] The dialysis membranes now being brought on the market, because of the great demand and increased production, are almost universally unsuitable. The only reliable shells known to the writer are those which have been tested in Abderhalden's laboratory. They are sold by Rudolph Shoepps, Halle, a. s.

THE COMPLEMENT-FIXATION TEST IN TYPHOID FEVER: ITS COMPARISON WITH THE AGGLUTINATION TEST AND BLOOD CULTURE METHOD.[1]

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The diagnosis of typhoid fever has always been a subject for extensive research. In spite of the many laboratory and immunity tests at our disposal (blood culture, agglutination test, leukocyte count and differential, ophthalmo-reaction, cutaneous reaction, diazo reaction, Russo test, cultures of urine, feces, etc.), the clinician is frequently desirous of other corroborative diagnostic methods. When a positive blood culture is obtained, further examinations are unnecessary. A number of our patients, however, come to the hospital after having been ill for some time; at this stage the bacteria are not so frequently detectable in the peripheral circulation. Furthermore, under conditions like too small veins, or inadequate equipment, as is the case out of town, the blood-culture method is less practicable, and the main reliance of diagnosis must be placed upon the Widal test or the leukocyte and differential count. The former is to a certain degree losing in its importance on account of the present favorable tendency toward prophylactic typhoid inoculations, which result in a strong agglutination power of the blood. The possibility of employing the complement-fixation method as a corroborative test in the diagnosis of typhoid fever has been often suggested. The author undertook a systematic investigation of

1. The frequency of its positive finding, its time of appearance and persistence.

2. Its comparison with the agglutination test and blood culture method.

3. Its occurrence after active immunization against typhoid fever.[2]

1. Bordet and Gengou[3] (1901) were the first to demonstrate complement-fixation bodies in the serum from two convalescent typhoid patients; as antigen a saline emulsion of typhoid bacteria grown for twenty-four hours was used. Since then numerous articles referring to this topic have been published, but the conclusions reached are various.

The most favorable reports are by Widal[4] and Lesourd,[5] who out

[1] Read at a meeting of the New York Serological Society, October 11, 1912.

[2] This is the subject of a separate paper in preparation.

[3] Annales de l'Institut Pasteur, 1901, xv, 290.

[4] Compt.-rend. de la Soc. Biolog., 1901, liii, 841.

[5] Recherch sur la présence d'un sensibilisatrice dans le serum des typhiques, Thèse, Paris, 1902.

of 61 patients obtained a positive result in 58. They were unable to repeat the test in the 3 negative cases.

Lüdke[6] examined 30 patients at a time during the acute illness when the temperatures were of the high continuous type and found 7 negative; 14 cases had to be examined twice. He does not therefore attribute much importance to the diagnostic value of the test.

Posner[7] advises against its introduction because several cases gave a negative reaction, although the Widal test was positive.

Spät and Zupnik[8] report out of 18 typhoid patients, 11 positive. They found the blood culture more reliable.

Hirschfeld[9] found positive reactions in all of 15 cases. Undoubtedly this wide difference of opinion is dependent upon variation in the technique of the complement-fixation test, but to the greatest degree upon the preparation of the antigen. Here all possible modifications exist.

The oldest and most reliable antigen is the watery extract of the bacteria, advised by Wassermann and Bruck.[10] This antigen was used with excellent results in the typhoid complement-fixation studies by Hirschfeld,[11] Leuchs,[12] and Raskin.[13]

Moreschi[14] as well as Bordet and Gengou[15] used saline suspensions of typhoid bacteria.

Ficker's reagent was employed by Van Loghem;[16] Chantemesse's vaccine by Spät and Zupnik.[17] Kentzler and Kiralypi[18] prepare an ether extract of the bacteria.

The author's antigen was made according to Wassermann-Citron's[19] directions for preparing artificial aqueous aggressins. Cultures are grown for twenty-four hours upon agar slants or plates (Kolle's flasks are preferable). The growth is washed off with sterile distilled water about 1 c.c to an agar slant., The total emulsion is kept in a hot-water bath at a temperature of 60° to 65° C. for twenty-four hours, then transferred to a strong bottle and shaken vigorously with the aid of glass beads for twenty-four hours. The bacteria are thus thoroughly broken up. The mixture is next centrifugalized for a long time (four to eight hours depending upon the total quantity) until all the bacteria have sunk to the bottom and the supernatant fluid is absolutely clear. The latter is carefully pipetted off, and can be preserved for about six to eight months in sealed tubes, not exposed to sunlight or room temperature. Sterile precautions must be taken throughout the preparation. The object of using a total small quantity of distilled water is to

[6] Handbuch, Kraus and Levaditi.
[7] Berl. klin. Woch., 1908, No. 37.
[8] Berl. klin. Woch., 1908, No. 40.
[9] Zeitsch. f. klin. Med., 1907, Band lxi, Heft 3–4.
[10] Med. Klin., 1905, No. 55
[11] Loc. cit.
[12] Berl. klin. Woch., 1907, Nos. 3 and 4.
[13] Centralbl. f. Bakt., Band xlviii, Heft 4, p. 508.
[14] Berl. klin. Woch., 1906, No. 38, p. 1243.
[15] Loc. cit.
[16] Centralbl. f. Bakteriol., Band xlv, Heft 6, p. 190
[17] Loc. cit.
[18] Zeitsch. f. klin. Med., 1908, Band lxv.
[19] Immunity, Methods of Diagnosis and Therapy, Blakiston's Son Co., Philadelphia, 1913.

eliminate the hemolysis of red-blood cells, which may be occasioned by employing large doses of antigen in the test.

It is best to titrate the strength of the antigen about one week after its preparation, as after the end of this period its titer usually remains unchanged. Varying quantities of antigen are mixed with the constant units of complement, hemolysin, and red cells (sheep system), and those amounts are determined which do not of their own accord inhibit hemolysis.

TITRATION OF ANTIGEN.

Typhoid antigen.	Complement.	Hemolysin.	Red blood cells.	Saline.	Result.
c.c.	c.c.	c.c.	c.c.	c.c.	
0.2	0.5 (1 to 10)	0.5 (1 to 1000)	0.5 (1 to 20)	Up to 2.5	No hemolysis
0.1	0.5 (1 to 10)	0.5 (1 to 1000)	0.5 (1 to 20)	....	No hemolysis
0.05	0.5 (1 to 10)	0.5 (1 to 1000)	0.5 (1 to 20)	....	Hemolysis complete
0.025	0.5 (1 to 10)	0.5 (1 to 1000)	0.5 (1 to 20)	....	Hemolysis complete
0.0125	0.5 (1 to 10)	0.5 (1 to 1000)	0.5 (1 to 20)	....	Hemolysis complete
0.00625	0.5 (1 to 10)	0.5 (1 to 1000)	0.5 (1 to 20)	....	Hemolysis complete

In accordance with the summation law of Weil and Nakayama,[20] the dose of antigen to be employed in complement-fixation experiments is represented by one-half of the maximum quantity of antigen that does not of itself bind complement; that is, in the above instance one-half of 0.05 c.c., or 0.025 c.c., or 0.5 c.c. of a dilution 1 to 20. This unit of antigen is then tested with a known typhoid serum to prove that complement-fixation is possible.

Just as has been demonstrated by Teague and Torrey[21] and Schwartz and McNeil,[22] that for gonococcus complement-fixation work a polyvalent gonococcus antigen is necessary, and by Austrian[23] that for the typhoid ophthalmo-reaction a highly polyvalent typhoid extract is essential, so is it also of fundamental importance, in order to obtain the greatest number of positive results with the typhoid complement-fixation experiments, to have an antigen prepared from a large number of different typhoid strains. The writer is absolutely convinced of this fact. The following case proves this:

Richard, aged nine years, was admitted to the medical service of Dr. Hensel at the German Hospital in August, 1912. Probable diagnosis was typhoid fever. The blood culture disclosed bacillus typhosus, the Widal test in dilution 1 to 50 was positive in one-half hour, but the complement-fixation test was negative. It was repeated several times at intervals of a week, but remained negative. The fourth time (during the convalescence) the reaction was only doubtful. This finding seemed exceptional in comparison with the other results. An antigen was therefore prepared from the patient's own typhoid strain; the complement-fixation test performed with his own extract was strongly positive, and with

[20] Münch. med. Woch., 1906, No. 21.
[21] Jour. Med. Res., 1907, No. 17.
[22] AMER. JOUR. MED. SCI., May, 1911.
[23] Johns Hopkins Bulletin, January, 1911.

the stock antigen prepared from seven different strains was doubtful; thus:

Stock antigen.	Patient's serum.	Complement.	Hemolysin.	Red cells.	Result.
0.025 c.c.	0.1 c.c.	0.5 c.c.	0.5 c.c.	0.5 c.c.	±
0.05 c.c.	...	0.5 c.c.	0.5 c.c.	0.5 c.c.	−
Antigen prepared from patient's own bacteria.					
0.02 c.c.	0.1 c.c.	0.5 c.c.	0.5 c.c.	0.5 c.c.	++
0.01 c.c.	0.1 c.c.	0.5 c.c.	0.5 c.c.	0.5 c.c.	++
0.005 c.c.	0.1 c.c.	0.5 c.c.	0.5 c.c.	0.5 c.c.	+
0.04 c.c.	...	0.5 c.c.	0.5 c.c.	0.5 c.c.	−
...	0.2 c.c.	0.5 c.c.	0.5 c.c.	0.5 c.c.	−
	Known typhoid serum.				
Antigen.					
0.025 (stock)	0.1 c.c.	0.5 c.c.	0.5 c.c.	0.5 c.c.	++
0.02 (patient's)	0.1 c.c.	0.5 c.c.	0.5 c.c.	0.5 c.c.	++
	Known negative serum.				
0.025 (stock)	0.1 c.c.	0.5 c.c.	0.5 c.c.	0.5 c.c.	−
0.02 (patient's)	0.1 c.c.	0.5 c.c.	0.5 c.c.	0.5 c.c.	−

On reviewing the literature, the author has found that this question of specificity has been worked out experimentally by Raskin.[24] Rabbits were immunized against typhoid bacteria, each animal receiving a different strain. While the antibodies of some strains would react with an antigen made from another strain, the opposite also took place; that is, the antibodies produced by one strain would fix complement only with an extract made from that particular strain. The agglutination test was less specific.

On account of this apparent marked difference, the antigen used in the latter part of the author's (Garbat) complement-fixation work was prepared from twenty-seven different typhoid strains isolated from former patients at the hospital. (Even this number of strains could be increased.)

The *technique* of the typhoid complement-fixation reaction is the same as that in the Citron modification of the original Wassermann test, but one-half the quantities are employed:

TECHNIQUE OF THE REACTION.

Antigen.	Serum from X.	Complement.	Hemolysin.	Sheeps' red cells.	Result.
c.c.	c.c.	c.c.	c.c.	c.c.	
(1) 0.025	0.1	0.5 (1 to 10)	0.5 (1 to 1000)	0.5 (1 to 20)	No hemolysis
(2) 0.0125	0.05	0.5 (1 to 10)	0.5 (1 to 1000)	0.5 (1 to 20)	No hemolysis
(3)	0.1	0.5 (1 to 10)	0.5 (1 to 1000)	0.5 (1 to 20)	Hemolysis
Controls.	Known typhoid serum.				
(1) 0.025	0.1	0.5 (1 to 10)	0.5 (1 to 1000)	0.5 (1 to 20)	No hemolysis
(2) 0.0125	0.05	0.5 (1 to 10)	0.5 (1 to 1000)	0.5 (1 to 20)	No hemolysis
(3)	0.1	0.5 (1 to 10)	0.5 (1 to 1000)	0.5 (1 to 20)	Hemolysis
	Known negative serum.				
(1) 0.025	0.1	0.5 (1 to 10)	0.5 (1 to 1000)	0.5 (1 to 20)	Hemolysis
(2) 0.0125	0.05	0.5 (1 to 10)	0.5 (1 to 1000)	0.5 (1 to 20)	Hemolysis
(3)	0.1	0.5 (1 to 10)	0.5 (1 to 1000)	0.5 (1 to 20)	Hemolysis
(4) 0.5	....	0.5 (1 to 10)	0.5 (1 to 1000)	0.5 (1 to 20)	Hemolysis

[24] Loc. cit.

List of Cases Examined.[25]

No.	Date.	Stage of disease.	Widal test.	Blood culture.	First complement-fixation test.	Second complement-fixation test.	Third complement-fixation test.	Fourth complement-fixation test.	Remarks.
3	July 23, 1912	First to second week	+	+	4+	.....	.....	.....	Died. Autopsy showed beginning swelling of Peyer's patches.
6	Aug. 2, 1912	" "	−	+	2+				
11	Aug. 6, 1912	" "	+	+	−	Aug. 14, −	Aug. 21, −		
22	Sept. 14, 1912	" "	±	+	1+	Aug. 22, 3+	Sept. 2, 4+	Aug. 28, +	
24	Sept. 20, 1912	" "	+	+	±	Sept. 27, +	Oct. 4, 3+		
26	Sept. 20, 1912	" "	+	+	2+	Sept. 27, 3+	Oct. 4, 4+		
4	Aug. 2, 1912	Second week	+	−	4+				
10	Aug. 10, 1912	"	±	+	−	Aug. 14, −	Aug. 21, 2+	Aug. 31, 4+	
12	Aug. 14, 1912	"	−	−	4+				
13	Aug. 14, 1912	"	−	−	−	Aug. 21, Widal, − Blood culture, − Complement-fixation test, −	Aug. 28, Widal, ± Blood culture, − Complement fixation test, 3+	Sept. 3, Widal, + Complement-fixation test, 3+	A very severe irregular typhoid. Died.
19	Aug. 28, 1912	"	+	+	3+				
21	Sept. 10, 1912	"	+	+	−				
25	Sept. 20, 1912	"	+	+	3+	Sept. 14, −	Sept. 20, 2+		
27	Sept. 20, 1912	"	+	−	−				
28	Sept. 27, 1912	"	+	+	−	Oct. 4, 2+			
29	Sept. 27, 1912	"	±	+	3+	Oct. 4, 2+			
34	Dec. 6, 1912	"	−	+	...				
35	Dec. 27, 1912	"	+	+	−	Dec. 13, 4+			
36	May 9, 1913	Third week	+	−	4+	Jan. 4, −	Mar. 3, 4+		
33	Nov. 28, 1912	"	+	+	4+				
23	Sept. 14, 1912	"	+	−	2+				
5	Aug. 2, 1912	"	+	−	4+				
9	Aug. 6, 1912	"	+	+	3+				
14	Aug. 14, 1912	"	+	−	4+				
16	Aug. 28, 1912	"	+	−	4+				
17	Aug. 28, 1912	"	+	−	3+				
18	Aug. 28, 1912	"	+	−	1+	Sept. 10, 3+			
20	Aug. 28, 1912	"	±	−	−	.....	.....	.....	Died before repeating test. Typhoid bacteria isolated from spleen.
32	Nov. 28, 1912	Fourth week	+	−	2+				
8	Aug. 6, 1912	"	+	−	4+				
37	May 9, 1913	Eighth week	+	−	4+				
30	Sept. 27, 1912	Convalescent	..	..	4+	.....	.....	.....	At first diagnosed as miliary tuberculosis. Recovered.
31	Sept. 27, 1912	"	+	..	4+				
1	July 23, 1912	"	..	..	4+				
2	July 23, 1912	"	..	..	4+				
7	Aug. 6, 1912	"	..	..	4+				
15	Aug. 21, 1912	"	+	−	2+				

[25] Tabulated according to the stage of infection.

The results are reported as 4+, 3+, 2+, 1+, ±, and −, but no definite diagnosis was made on a 1+ or ± reaction. A reaction is 1+ when there is no hemolysis in tubes 1 or 2; 3+ when no hemolysis in 1, and slight hemolysis in 2; 2+ when no hemolysis in 1, and complete hemolysis in 2; 1+ when slight hemolysis in 1, and complete hemolysis in 2; ± when faint turbidity is present in 1; − when complete hemolysis exists in both 1 and 2.

In this manner 37 cases were examined in the various stages of the typhoid infection from the early onset to the late convalescent period. Out of this group, 36 sooner or later gave a strong positive reaction. If negative, the reaction was repeated every five to seven days.

25 were positive on the first examination.
5 became positive on the second examination.
5 became positive on the third examination.
1 became positive on the fourth examination.
1 remained negative. This patient died several days after admission to the hospital, so that the test was not repeated.

How Early in the Infection May the Complement-fixation Bodies Be Detected in the Blood? This answer is difficult, because of the inexactness associated with telling in what stage of the disease the patient is at a particular time. Each clinician has his own method of calculation. In the above table the author estimated this period, by counting back from the onset of abnormal temperature. That the complement-fixation test may be obtained in a very early stage of the disease was proved by Case 3, where the patient died of an extreme toxemia, and at autopsy the Peyer's patches were found just beginning to become swollen; surely not later than the end of the first or early part of the second week. In the majority of instances, however, the reaction appears toward the end of the second or early part of the third week (at a time when the blood culture tends to be negative), and becomes stronger as the disease advances toward convalescence. From the above statistics:

No of cases.	Stage of disease.	Positive results (at the first examination).
18	First and second weeks	8, or 45 per cent.
19	After second week	17, or 90 per cent.

Lüdke[26] too has found that the test appears during the second week. Hirschfeld[27] reports a positive reaction as early as the sixth to the eighth day of the infection.

How Long after the Acute Infection Does the Positive Test Persist? A greater number of cases would, of course, enable us to give a more conclusive and definite answer. As a general rule, the reaction is still obtained, and very strongly so too, six to eight weeks after the temperature has become normal. In two patients it was still

[26] Loc. cit.

[27] Loc. cit.

positive four months afterward. One of these became a typhoid carrier with bacteria in the urine. Three patients who had typhoid fever two years previously, gave a negative reaction, although in one the Widal test was still positive (1 to 50). One patient who had an infection seven years ago and one fifteen years ago were negative. It would be of importance to test this reaction in the blood of typhoid carriers, especially those of long standing. Schöne[28] reports three such. One a carrier of ten years' standing, the second of three and one-half years, and the third of three months' duration. In all the fixation was positive. Agglutinins were present only in the third.

Throughout the experiments it seemed that individuals who ran a severe or protracted type of disease developed the complement-fixation bodies less readily or later in the course than the others. While this fact holds true in a great number of instances, it cannot, however, be advocated as a guiding principle of prognosis. Thus Case 3, where the patient had a most severe infection and died several days after admission to the hospital, the complement-fixation test was strongly positive, even though, as was proved by postmortem examination, the patient was at the end of the first or beginning of the second week of the disease.

As to the clinical specificity of the reaction, sera from patients with the following diseases have been tested: La grippe, gastro-duodenitis, trichiniasis, syphilis in the various stages treated and untreated, malaria, tuberculosis, pneumonia, perinephritic abscess, appendicitis, plumbism, and pelvic abscess. Numerous normal sera were also controlled. All gave a negative reaction. Occasionally a doubtful result would be noted, but never a distinct inhibition of hemolysis. One patient with an infective endocarditis, from whose blood the Streptococcus viridans was isolated, gave a positive (++) reaction on one examination, but repetition of the test with another specimen of blood taken in several days elicited a negative result. Another patient with a marked mitral endocarditis, no bacteria in the blood and only slight temperature, repeatedly gave a strong positive reaction. A history of several weeks' illness at home with high fever was obtained, but no definite diagnosis of typhoid fever. The possibility of this protracted illness having been typhoid, with the endocarditis as a sequel (there being no other distinct etiological factor) was strongly suspected. In another instance the complement-fixation test proved even more specific than the agglutination test. The serum from a case of Staphylococcus aureus sepsis with multiple abscesses of the kidney, gave an agglutination with typhoid bacteria, in dilution 1 to 50, but no complement-fixation test. (At postmortem no evidences of a typhoid infection could be discovered).

[28] Münch. med. Woch., 1908, No. 20.

In 32 cases sufficient blood was taken at the first examination for the complement-fixation test, the Widal test, and the blood culture, so that comparative studies of the three could be made (see Table). Tabulated according to parallel results obtained, out of 18 cases during the first and second weeks of the disease and 14 cases more advanced there were:

Total number.	First and second weeks.	Later than second week.	Widal test.	Blood culture.	Complement-fixation test.
12	1	11	+	−	+
6	4	2	+	+	+
5	5	—	+	+	−
3	3	—	−	+	+
2	2	—	−	+	−
2	2	—	−	−	+
1	1	—	+	−	−
1	1	—	−	−	−

It is observed that there is no absolute uniformity in these findings. All possible combinations may occur, especially in the early stages of the disease. In the later stages, however, the general rule was a positive Widal and complement-fixation test and a negative blood culture.

If one considers the frequency with which each test by itself was positive, the following is noted:

Widal . . . . . + in 24 cases (11 out of 18 in first two weeks, 13 out of 14 later on)
Blood culture . . . . + in 16 cases (14 out of 18 in first two weeks, 2 out of 14 later on)
Complement-fixation . + in 23 cases (10 out of 18 in first two weeks, 13 out of 14 later on)

Thus complement fixation was present as frequently as the positive Widal test, and was then of great corroborative value. In two cases (12 and 13) it was positive even before the Widal or the blood culture. Similar experiences are reported by Spät[29] and Hirschfeld.[30] That the blood culture was positive in only 50 per cent. of our cases is probably accounted for by the better class of our ward patients. They are treated at home for a longer period of time, and thus come to the hospital when there is less likelihood of still finding the bacteria in the blood.

In conclusion the following summary may be given:

1. Practically all typhoid fever patients examined, sooner or later developed antibodies in their serum, which were demonstrable by the method of complement-fixation. These bodies increase in number with the progress of the disease and are especially numerous during convalescence.

2. A highly polyvalent antigen properly prepared is absolutely essential in order to obtain a maximum of positive results.

3. Strains of typhoid bacteria may differ from each other in that their respective antibodies cannot fix complement with an antigen made from a different strain.[31]

[29] Loc. cit. [30] Loc. cit.

[31] With this experience in mind, the author has always employed a polyvalent typhoid vaccine for prophylactic antityphoid inoculations.

4. There is no definite relationship between the occurrence of a positive Widal and complement fixation test on one hand with a positive blood culture on the other.

5. When the blood culture is negative, as so frequently happens in the later stages of typhoid fever, a positive complement-fixation test throws great corroborative diagnostic weight on the side of a doubtful or positive Widal reaction. Occasionally the test is positive before the Widal or blood culture.

6. The very simple technique for obtaining 1 c.c. of blood from the patient's ear or finger when the veins are not suitable, stands out prominently in contrast to the extensive, and at times impossible preparations required for a blood culture. The ease of transportation of the specimen of blood must also be considered.

The writer must thank the medical attendings of the hospital for granting him the privilege of these examinations. Without their kind and constant coöperation this work would have been impossible.

RELATION OF LESIONS OF THE SMALL INTESTINE TO DISORDERS OF THE STOMACH AND CAP AS OBSERVED ROENTGENOLOGICALLY.

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The relation of lesions of the small intestine to disorders of the stomach has been recognized for many years by clinicians, most notably perhaps in the vomiting, pain, and tenderness referred to the right hypochondrium in cases of appendicitis, and in the gastric symptoms manifested by acute intestinal obstruction. Mayo has compared the stomach to a fire-alarm box, and has called attention to the futility of trying to extinguish the fire by squirting water on the alarm box. In a recent article read before the American Roentgen Ray Association,[1] Crane quoted Mayo's simile, and cited instances in which he also had observed gastro-intestinal symptoms with roentgenological evidence of a lesion at some distant point. In this communication I shall try to show that the roentgenologist can detect the first sign of smoke, and after searching farther, can usually find the location of the fire itself.

Terminology. Before entering upon any discussion an explanatory word should be said concerning terminology. While the roentgenological findings of the gastro-intestinal tract differ in every individual, I have come to recognize certain findings as

[1] Boston, October, 1913.

usual and others as unusual. In this communication the term *usual* will be applied to those findings which are most common, that is to say, normal, so far as I have been able to determine, and the term *unusual* will be applied to uncommon roentgenographic findings, which are associated with symptoms.

THESIS. As a working basis it will be necessary to describe the physiology of the duodenum, jejunum, and ileum as observed roentgenologically, and to compare the unusual findings with the usual findings. It will be seen that certain phenomena in the small intestine are frequently accompanied by peculiar manifestations in the stomach and cap. These gastric manifestations, viz., primary and secondary evidences of spasm and their opposites, atony or lack of peristalsis of the pylorus, pyloric sphincter and cap, must next be described. Upon this foundation we shall build up the superstructure which is the main subject of this communication—that iliac stasis, and particularly iliac dilatation, are directly related to and responsible for certain spasms and even organic lesions of the pylorus, pyloric sphincter, and cap. In conclusion, we shall estimate the value of the roentgenological evidence for determining in each individual case whether or not surgical procedure is indicated, or what other method of treatment is advisable.

TECHNIQUE. In order to obtain the findings upon which our observations are based, an extensive routine examination of the entire gastro-intestinal tract is essential. Although the technique employed is being elaborated continually, a brief description of the present method may be of interest.

About 11 P.M., or ten hours before the roentgenographical examination, the patient takes bismuth or barium suspended in buttermilk, in conjunction with a meal of meat, potatoes, and bread. At 9 o'clock the next morning he presents himself for examination. A roentgenogram of the whole abdomen is made to determine how far the meal taken the night before has progressed. This information can usually be obtained from the fluoroscopic examination, which is made simultaneously; but if any doubt exists the plate should be developed rapidly in order to ascertain with certainty whether or not the ileum is empty. If food still remains in the ileum the same examination is repeated bi-hourly until the ileum is completely evacuated, then the patient takes bismuth or barium suspended in buttermilk. After the passage of the ingesta through the esophagus has been observed fluoroscopically the stomach is examined by combined fluoroscopy and serial roentgenography.

SERIAL ROENTGENOGRAPHY OF THE STOMACH. Twelve roentgenograms are made in the prone posture, four to six in the lateral direction, two posteriorly, and twelve with the patient erect, after which the patient at once eats a meal of meat, potatoes, and bread. Two hours later another series of six to twelve roentgeno-

grams is made, two of them stereoscopic roentgenograms of the entire gastro-intestinal tract. As this series often gives the most valuable information, we are therefore increasing the number of exposures made at this time. If further details concerning the progress of gastric digestion seem desirable, another series of roentgenograms is made four hours after ingestion. A pair of stereoroentgenograms is invariably taken six hours after the bismuth meal. If at this time the fluoroscope reveals an appreciable gastric retention, five or six roentgenograms of the stomach are made.

EXAMINATION OF ILEOCECAL REGION. — As the condition of filling in the ileocecal region is of prime diagnostic importance at this time, two small stereoroentgenograms (8 x 10 inches) are made of this portion of the tract, and if marked stasis or any other unusual finding is observed fluoroscopically, six to eight small roentgenograms of this region are made. Two hours later, *i. e.*, eight hours after ingestion, one plain roentgenogram or a pair of stereoroentgenograms is made. This completes the examination for that day. At nine o'clock the next morning, *i. e.*, twenty-four hours after the ingestion of bismuth and buttermilk, another roentgenogram is obtained. If there is evidence of colonic stasis or constipation a roentgenogram is made every twenty-four hours until the colon is evacuated. In case the patient habitually depends upon a cathartic, it should be allowed as usual, but an active purgative is undesirable.

After the examination just described there remains to be made an examination of the gall-bladder for possible calculi, and also an examination of the colon, while mechanically distended, for the purpose of discovering any spasmodic or organic lesions not detected when the bismuth passed through from above.

The night before this examination an active cathartic is administered. If this is not effective the patient takes a saline cathartic early in the morning, but on no account an enema, as this might be retained and dilute the bismuth clyster, which is used to distend the colon.

EXAMINATION OF GALL-BLADDER. Before the colon is examined, roentgenograms are made over the gall-bladder region, as biliary calculi can be detected in at least 50 per cent. of the cases when they are present.[2]

EXAMINATION OF THE COLON. A clyster of bismuth or barium, mucilage of acacia, and hot water (barium sulphate ℥v, mucilage

[2] Case, The X-ray Examination of the Liver and Gall-bladder, Arch. of Roent. Ray., September, 1913; Roentgenoscopy of the Liver and Biliary Passages, with Special Reference to Gall-stones, Jour. Amer. Med. Assoc., September 20, 1913. Cole, Roentgenographic Diagnosis of Gall-stones and Cholecystitis, Surg., Gyn., and Obst., February, 1914, vol. xviii, No. 2. Pfahler, Die Roentgenstrahlen als Hilfsmittel bei der Gallensteindiagnose, Fort. a. d. Geb. d. Roent., April, 1911. N.H., xvi, B. 5, pp. 335-337. Gastric and Duodenal Adhesions in the Gall-bladder Region and Their Diagnosis by the Roentgen Ray, Jour. Amer. Med. Assoc., June 17, 1911, vol. lvi, No. 24, pp. 1777-1779.

of acacia ℥xij, hot water q. s., ℥xxx) is now administered and retained by the patient while a pair of stereoroentgenograms of the colon are made. It is a wise procedure to make a third plain roentgenogram or another pair of stereoroentgenograms, because it is sometimes difficult to differentiate between spasms and organic lesions in a single pair of stereoroentgenograms.

The gastro-intestinal tract has now been completely examined by successive series of roentgenograms made immediately after the bismuth meal, and at intervals thereafter of two hours, four hours, six hours, eight hours, ten hours, twelve and fourteen hours twenty-four hours (if necessary), forty-eight hours, and seventy-two hours, and by one or more pairs of stereoroentgenograms of the colon, made after a bismuth clyster has been administered.

Such a series of roentgenograms, viewed upon a light box, where they may be studied individually and collectively, gives a wealth of information. By carefully studying the findings in one region and comparing them with the findings in other portions of the tract it is often possible to unravel the most complicated cases.

Value of Complete Gastro-intestinal Examination. A study of about 300 such cases, showing the stomach, small intestine, and colon at various intervals after the ingestion of food, has revealed a great variety of significant findings, a correlation of which leads me to the publication of this preliminary report.

Erroneous Methods of Determining Gastro-intestinal Motor Efficiency. Many of the previous roentgenological observations on iliac stasis have been unreliable, because the bismuth has been mixed with or suspended in unsuitable mediums, and because the period required for iliac evacuation has been reckoned from the time when the bismuth was administered, instead of being reckoned from the time when the last trace of it left the stomach. Other conditions, such as recent catharsis, which so often precedes a gastro-intestinal examination, undoubtedly affect the motor phenomena.

In a previous communication[3] I have already shown the fallacy of testing the gastric motor efficiency by administering bismuth suspended in fluid or mixed with cereal, and the same is true for intestinal motor efficiency. If the test is to be of value the stomach and intestines must be called upon to evacuate such a meal as is normally imposed upon them. Therefore the true test of gastro-intestinal motor efficiency is made by administering bismuth or barium, suspended in fluid, preferably buttermilk, *in conjunction with* a Riegel meal of meat, potatoes, and bread.

An even more fertile source of error is dating the period of iliac retention from the time of ingestion. For instance, if the stomach

[3] Die Diagnose der Boesartigen und Gutartigen Magen—und Duodenal-Laesionen und ihre Unterscheidung durch Serien-Roentgen-Aufnahmen, Zeitschrift f. klinische Medicin, Berlin, 1914, 79, B. H., 5 u. 6.

is high and of the cow-horn type, especially if a condition of diminished acidity or achylia exists, evacuation will be accomplished very rapidly, perhaps in two hours, whereas many a stomach, presenting no organic obstruction, requires six hours for complete evacuation. Suppose now that in both cases the ileum is just evacuated ten hours after ingestion. According to the old method of reckoning, both cases present the same degree of iliac stasis, although, as a matter of fact, one case presents an eight-hour while the other presents only a four-hour iliac retention. The time required for bismuth impregnated food to pass through the small intestine may be corroborated by reckoning the speed with which the next succeeding meal, not impregnated with bismuth, displaces that previously ingested, or mixes with it at the cecum.

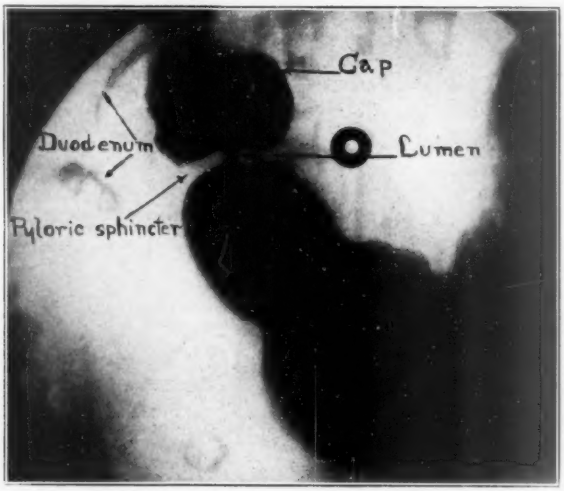

FIG. 1.—Normal cap (pilleus ventriculi).

KNOWLEDGE OF ROENTGENOLOGY OF THE STOMACH AND CAP AN ESSENTIAL TO AN UNDERSTANDING OF THIS COMMUNICATION. In previous communications, which are, in a way, introductory chapters to the present work. The physiological characteristics and motor phenomena of the pyloric sphincter and pilleus ventriculi (cap)[4] as observed roentgenographically has been described. In fact this information constitutes the *sine qua non* of roentgenological diagnosis of the gastro-intestinal tract. It has been shown

[4] Arch. of Roent. Ray, December, 1911, p. 242; Amer. Quart. of Roent., March, 1912, vol. iii, No. 4, p. 1. Arch of Roent. Ray, October, 1912, No. 147, p. 172; Jour. Amer. Med. Assoc., November 30, 1912, vol. lix, p. 1947.

that the region previously termed the first or ascending portion of the duodenum is not the duodenum in any sense, but is actually the cap of the stomach (pilleus ventriculi) (Fig. 1). Its anatomy and physiology as observed roentgenologically and the lesions to which it is subject have been described.[5] Therefore in this communication we may begin with the descending portion of the duodenum.

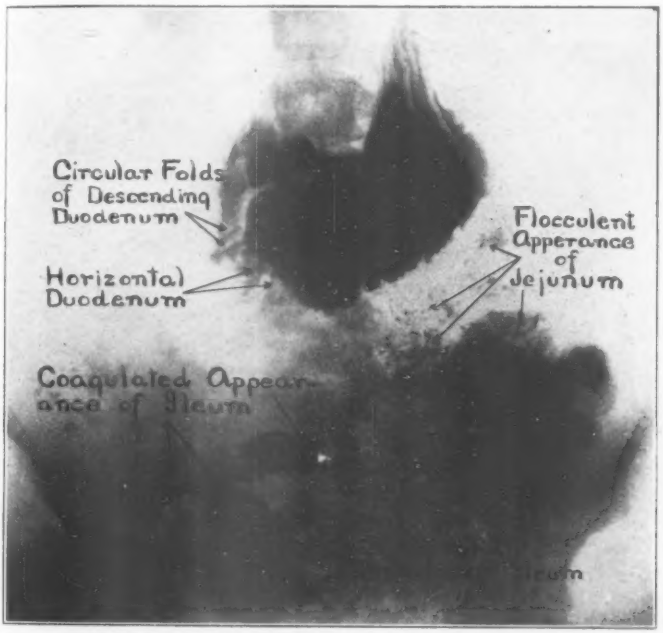

FIG. 2.—Usual roentgenographical appearance of cap, duodenum, jejunum, and ileum.

USUAL FINDINGS IN THE DUODENUM. Embryologically the descending and not the ascending duodenum is the proximal end of the midgut. Anatomically it exhibits small, irregular, circular folds, particularly on its posterior aspect. It descends at an acute angle from the top of the cap, and in conjunction with the horizontal portion, fits around the head of the pancreas, occupying a fixed position. As it frequently passes down behind the stomach it may be obscured by the pars pylorica, except where it extends above and below the stomach. It can be identified by its shape, and position and the ring-like appearance of its circular contractions (Figs. 1, 2, and 3). Its motor phenomena is a broad, rapid,

[5] Arch. of Roent. Ray, April, 1912, No. 141, p. 425; Jour. Amer. Med. Assoc., September 6, 1913, vol. lxi, No. 10, p. 762.

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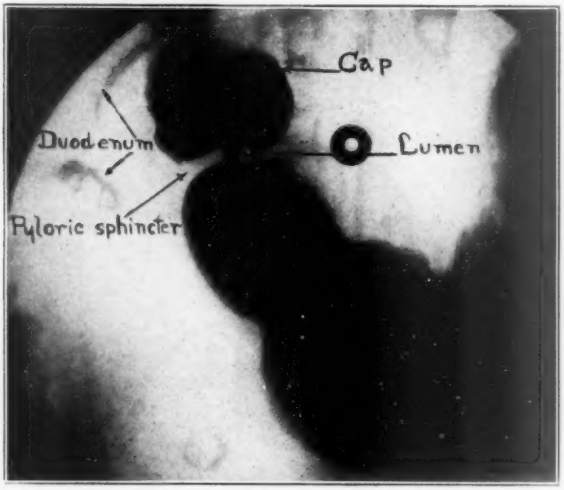

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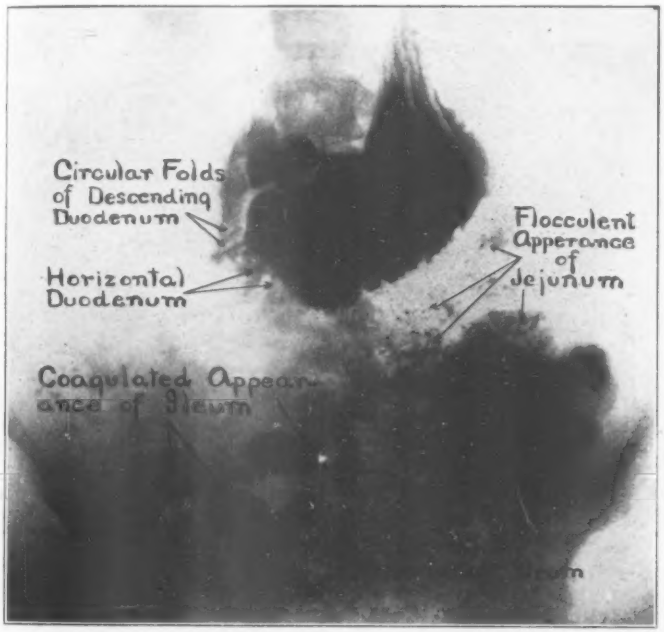

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periodical, propulsive peristalsis, and a churning or mixing motion of the circular folds.

USUAL FINDINGS OF THE JEJUNUM. From the horizontal duodenum the ingesta pass into the jejunum in the upper left quadrant of the abdomen, where they are broken up into finely comminuted particles. Roentgenographically these fragments present the flocculent appearance which distinguishes the jejunum from the rest of the small intestine (Figs. 2 and 3).

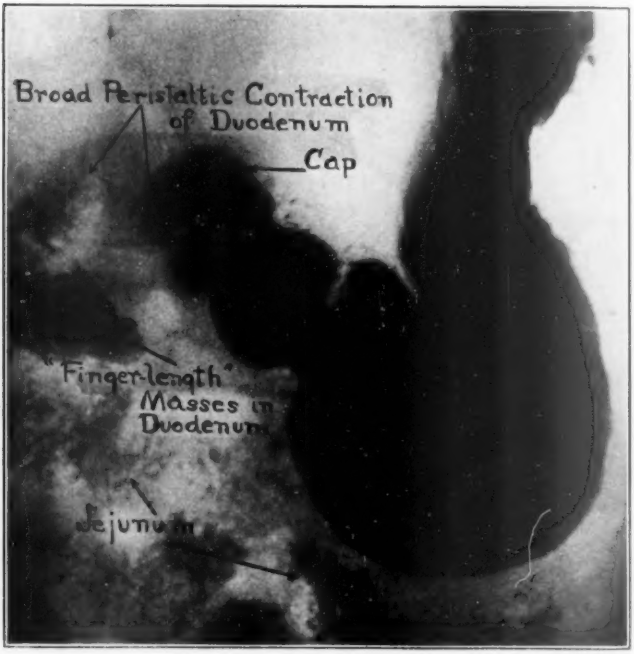

FIG. 3.—Withdrawal of chyme from cap by broad propulsive peristalsis of duodenum.

USUAL FINDINGS OF THE ILEUM. As the chyme reaches the centre of the small intestine and occupies the ileum it begins to form into coagulated masses. Upon reaching the terminal portion of the ileum these coagulated masses collect in long, worm-like coils, and as they near the cecum they fill the lumen of the gut, so that frequently one can identify several continuous convolutions of the ileum, especially if the roentgenograms are studied stereoscopically. The ileum, therefore, is recognized roentgenographically by its location in the right lower quadrant of the abdomen and the coagulated appearance of the contents in its upper portion (Fig. 2),

and the well-defined worm-like coils in its lower portion (Figs. 2, 10, 15, and 16).

PHYSIOLOGY OF THE SMALL INTESTINE AS OBSERVED ROENTGENOGRAPHICALLY. The characteristic roentgenographic findings by which the various portions of the small intestine may be thus identified are the result of certain physiological phenomena, expressed roentgenologically in terms of motor activity.

MOTOR PHENOMENA OF THE DUODENUM. The descending duodenum obtains the ingesta by means of broad peristaltic contractions (Fig. 3), which withdraw the chyme from the reservoir cap, where it collects after being expelled through the pyloric sphincter during the systole of each gastric cycle. Duodenal peristalsis occurs periodically, but not coincidentally with or at the same rate, as gastric peristalsis. The chyme is thus propelled through the duodenum in the finger-like masses described by Holzknecht (Fig. 3). During the early stage of digestion this process takes place very rapidly, because the contents of the cap are only slightly acid and mostly fluid, having been expelled through a more or less tightly contracted sphincter.

MOTOR PHENOMENA OF THE JEJUNUM. Roentgenographic observations have proved that the name jejunum was well chosen by the ancients from their postmortem investigations, for the peristalsis of this portion of the tract is so rapid that the jejunal lumen is seldom seen dilated or even filled.

MOTOR PHENOMENA OF THE ILEUM. The ileum retains the food longer than any other portion of the small intestine. It lodges here temporarily, after being passed rapidly through the cap, duodenum, and jejunum.

ROENTGENOLOGIC APPEARANCE OF SMALL INTESTINE PARTLY DUE TO CONSISTENCY OF CONTENTS. The flocculent appearance of the jejunum, coagulated appearance of the upper ileum, and worm-like coils of the lower ileum are probably caused, in part at least, by the consistency of the contents as well as by the peristalsis characteristic of each region. When a clyster passes back through an incomplete ileocecal valve, filling the ileum and even distending the jejunum, the roentgenological findings peculiar to different portions of the small intestine do not present.

UNUSUAL FINDINGS OBSERVED IN THE SMALL INTESTINE ILLUMINATE MANY OBSCURE FUNCTIONAL GASTRO-INTESTINAL LESIONS. Variations from the above-described motor phenomena of the small intestine cause unusual roentgenographical findings, which illuminate, I believe, many of the obscure functional and even organic disorders of the gastro-intestinal tract. A description of all of the roentgenological findings associated with functional gastric derangements would form an extensive communication in itself. In this paper we can only enumerate and briefly describe those usually associated with lesions of the ileocecal region. Such

functional gastric disorders present the following roentgenological findings:

1. Spasms of . . . . . { (*a*) the pars pylorica. (*b*) the pyloric sphincter. (*c*) the cap.
2. Results of spasms, indicated by permanent changes in . . . { (*a*) the pars pylorica. (*b*) the pyloric sphincter. (*c*) the cap.
3. Gastric retention without pylorospasm.

SPASMS OF THE PARS PYLORICA, PYLORIC SPHINCTER, AND CAP. There are two ways of ascertaining that the pars pylorica, pyloric sphincter, or cap is subject to spasmodic contraction. The spasm itself may be registered on some or all of the roentgenograms of the series in the very act of occluding the lumen. Or only the results of the spasm may be visible in a permanent diminution of the lumen, caused by constant or spasmodic contraction of the muscular coat.

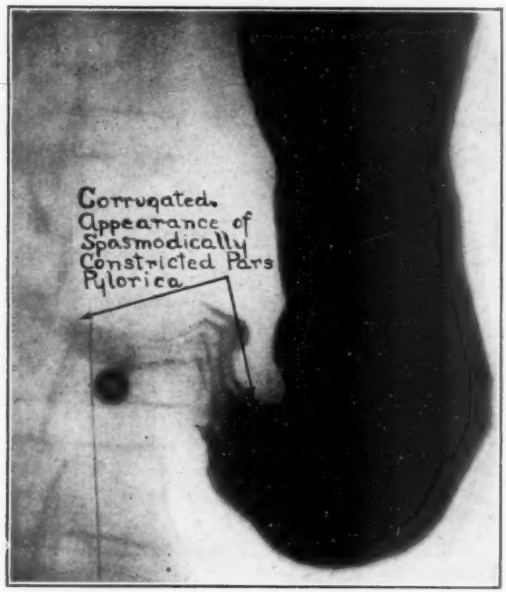

FIG. 4, *a*.—Spasmodic constriction of pars pylorica.

SPASM OF THE PARS PYLORICA. The roentgenographical picture of spasmodic contraction of the pars pylorica shows that portion of the gastric lumen reduced in size out of all proportion to the dimensions of the pars media and pars cardiaca. The whole or only the pyloric end of the region may be distorted. The mucosa and

submucosa, normally ribbed by shallow rugæ, are puckered into deep folds, which give the lumen a corrugated appearance (Fig. 4, *a*). These furrows may run transversely or obliquely. The roentgenogram which presents these phenomena may be followed by one showing a perfectly smooth, well-distended contour of the same region, indicating that the spasm has relaxed its grip temporarily (Fig. 4, *b*). Sometimes the spasm occurs only at a certain stage of digestion, and is absent in all the roentgenograms made before and after this interval.

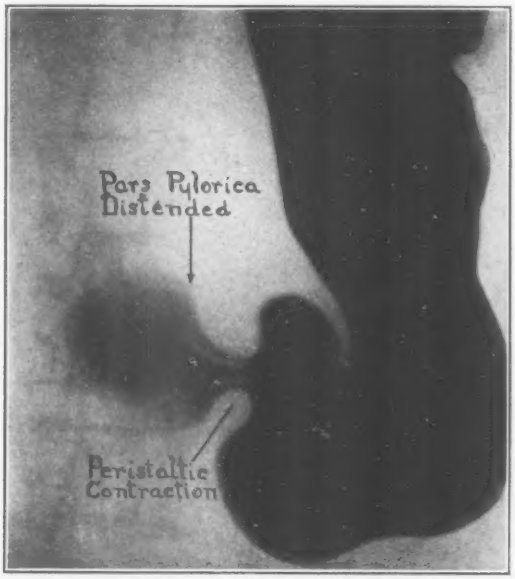

FIG. 4, *b*.—Relaxation of spasm illustrated in Fig. 4, *a*.

SPASM OF THE PYLORIC SPHINCTER. The presence of a spasmodic constriction of the pyloric sphincter may be inferred from the absence of bismuth in the lumen of the sphincter and cap, provided the bismuth is seen passing freely from the stomach into the cap in roentgenograms made previously and subsequently (Fig. 5, *a* and 5, *b*). If the cap is quickly evacuated by duodenal peristalsis, its outlines will remain indistinct or invisible until a relaxation of the pyloric sphincter opens the passage from the pars pylorica through which the cap is resupplied with contents.

In spite of Kreuzfuch's reports to the contrary, my observations have been that the gastric peristalsis may be just as active while a spasm involves the pyloric sphincter as it is when the sphincter is functionating normally.

SPASM OF THE CAP. Constriction of the cap from spasmodic contraction presents roentgenographical evidence similar to that

FIG. 5, *a*.—Spasmodic constriction of pyloric sphincter.

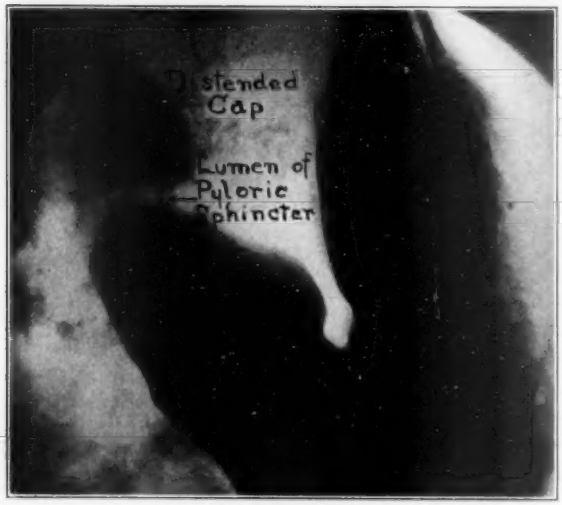

FIG. 5, *b*.—Relaxation of spasm illustrated in Fig. 5, *a*.

caused by a spasm of the colon. The cap has the appearance of having been twisted or wrung empty of its contents, only a sugges-

tion of its bismuth impregnated contents being visible, caught or entangled under the constricting folds. As a result the distorted lumen casts a corrugated or fluted shadow on the roentgenograms (Fig. 6). An interesting case of this kind, presenting definite symptoms of ulcer of the cap, was referred to me from a hospital for the sake of increasing the number of my postpyloric ulcer cases. The clinical history was so typical that I economized by making only about half the usual number of roentgenograms. Even this limited series proved enough to justify a negative diagnosis of chronic indurated duodenal ulcer, that is, an ulcer indicating surgical procedure. Most of the roentgenograms showed definite graphic evidence of a spasm of the cap. In two instances, however,

Fig. 6.—Spasmodic constriction of cap, caused by chronic appendicitis. Proved by operation.

a fully distended well-defined cap presented a perfectly normal picture. I therefore reported that the lesion was spasmodic rather than organic, although the spasm might possibly be caused by a superficial postpyloric ulcer. This negative report delayed operation for the duodenal ulcer, which had been diagnosed by other means. Two days later the patient's symptoms culminated in a definite attack of acute appendicitis, for which an emergency operation was performed. The clinical diagnosis of duodenal ulcer had been made so positively, and the history had been so definite that I permitted myself to dispense with a complete gastrointestinal examination, and allowed a preconceived theory to distract my mind from considering a lesion of the right iliac fossa

as the origin of the spasm, although in several previous cases I had recognized a similar interrelation. The moral of this is, "Don't let a perfectly typical history of some condition deter you from making a complete examination."

PERMANENT CHANGES IN THE PARS PYLORICA, PYLORIC SPHINCTER, AND CAP. All of the findings described thus far have been direct evidence of the spasm itself. Let us now consider the roentgenological findings of those permanent changes which result from long-continued spasms of the pars pylorica, pyloric sphincter, and cap.

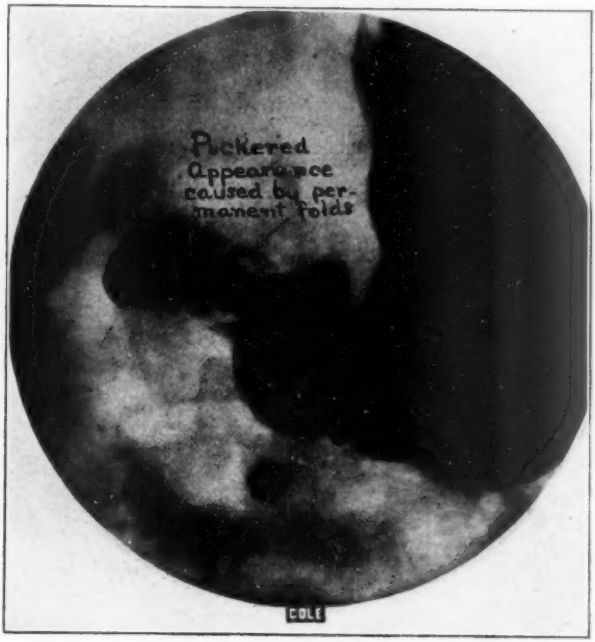

FIG. 7.—Permanent changes in gastric wall, resulting from long-continued spasm of pars pylorica. Proved by operation.

Frequent spasm of the pars pylorica causes a contraction of the muscular coat, and a consequent diminution of the lumen of this region as compared with lumen of the pars media and pars cardiaca. The mucosa and submucosa heap up into deep folds and attain a permanently puckered appearance, such as they formerly presented only when dominated by a spasm. The region lacks pliability, presenting unusually broad peristaltic contractions, but exhibits a regular systole and diastole (Fig. 7).

The result of spasm of the pyloric sphincter is not quite so characteristic. It may be described as a puckering resembling the folds near a purse string that had been tightly drawn, and is most prominent during the stage of diastole, when the adjacent tissue is completely relaxed (Fig. 8). The sphincter may be thicker than normal, but at some stage of digestion its lumen should be distinctly shown.

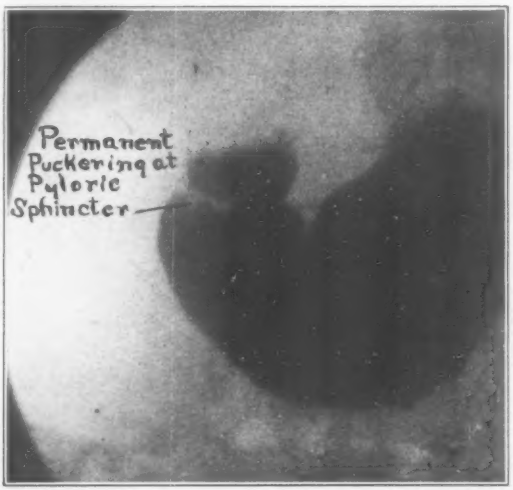

FIG. 8.—Permanent changes in pyloric sphincter, caused by constant spasmodic constriction, a reflex from chronic appendicitis. Proved by operation.

The roentgenological findings of permanent changes resulting from spasm of the cap are so similar to those of postpyloric ulcer that the two conditions are sometimes difficult to differentiate. Such a case is illustrated in Fig. 9. Roentgenographically the cap had the appearance of being cicatricially contracted by an ulcerative process, and the lesion was diagnosed as postpyloric ulcer. Operation revealed chronic appendicitis and redness and swelling of the cap near the pylorus without any evidence of ulceration, obviously the result of constant reflex spasmodic contraction from the diseased appendix.

GASTRIC RETENTION WITHOUT PYLOROSPASM. Having discussed overactivity of the muscularis as a functional lesion of the pars pylorica, pyloric sphincter and cap, let us now consider lack of activity of these same muscular tissues.

Although lack of tonicity is undoubtedly a functional disorder of the stomach, and as such is related to our subject, yet it is not

caused by a lesion at some distant point, so far as we know, and should therefore be omitted here.

FIG. 9.—Permanent changes in cap, resulting from long-continued spasm, a reflex from chronic appendicitis. Resembles the roentgenographical appearance of cicatricial contraction from postpyloric ulcer.

RETENTION IN STOMACH AND CAP DUE TO INHIBITION OF DUODENAL PERISTALSIS. Retention in the stomach and cap longer than the normal time required for digestion is a roentgenological finding of the utmost significance. As digestion progresses there often ensues a diminution or complete inhibition of propulsive duodenal peristalsis and evacuation of the cap is suspended temporarily (Fig. 10). At the same time gastric peristalsis may still continue and even increase its propulsive power, owing to the diminished bulk which it is gripping. Thus the cap, being rapidly filled from the stomach and not evacuated by the duodenal peristalsis, distends during the later stages of digestion to fuller proportions than before (Fig. 10). Sometimes the force of gastric peristalsis is sufficient to expel the chyme through the cap into the descending and horizontal duodenum, but so long as the jejunum remains empty, it is obvious that duodenojejunal peristalsis has stopped functionating. It is the absence of this agent for sucking the food from the cap and propelling it through the duodenum, which explains the gastric and cap retention in many instances, for it cannot be contended that there is any organic or functional disturbance of the stomach or cap, since the chyme courses through

them freely, nor is it tenable to suppose that any organic obstruction exists in the duodenum or jejunum, as the chyme rapidly traversed this region at an earlier stage of digestion.

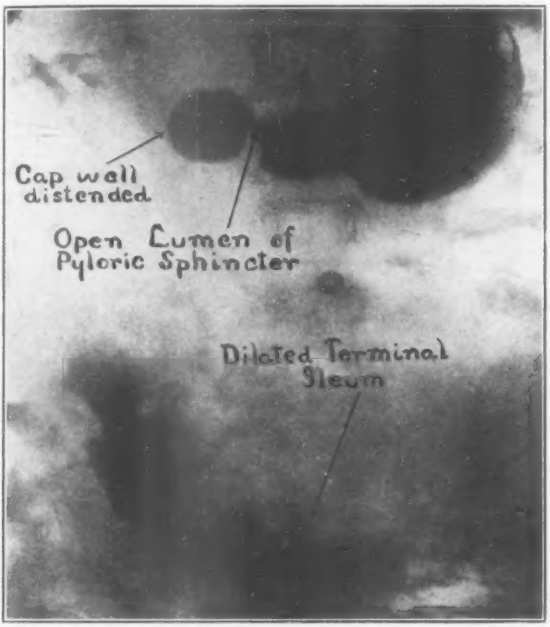

FIG. 10.—Dilatation of terminal ileum, causing inhibition of duodenal peristalsis and resultant gastric and cap retention.

DANGERS OF PROLONGED RETENTION IN THE CAP. Retention in the cap is often the harbinger of organic lesions of the right hypochondrium. It may cause conditions favorable for the production of postpyloric ulcer. As has been stated in previous communications the cap has the function of a reservoir or second stomach, where it is probable that the finishing touches of proteid digestion are applied to the small amount of chyme thus isolated from the bulk of food in the stomach. That the strength of the gastric juices is intensified in the cap may be inferred from the presence here of the glands of Brunner and Lieberkuhn. If duodenal peristalsis ceases after most of the chyme has been withdrawn from the stomach, and an appreciable amount of chyme remains in the cap for a much longer period of time that usual (Fig. 11), is it not reasonable to suppose that this chyme becomes hyperacid from oversaturation with the juices of the secretory glands of the cap? For if it is imprisoned in the cap without being diluted by

FIG. 11.—Prolonged retention in cap after evacuation of stomach, duodenum, and jejunum.

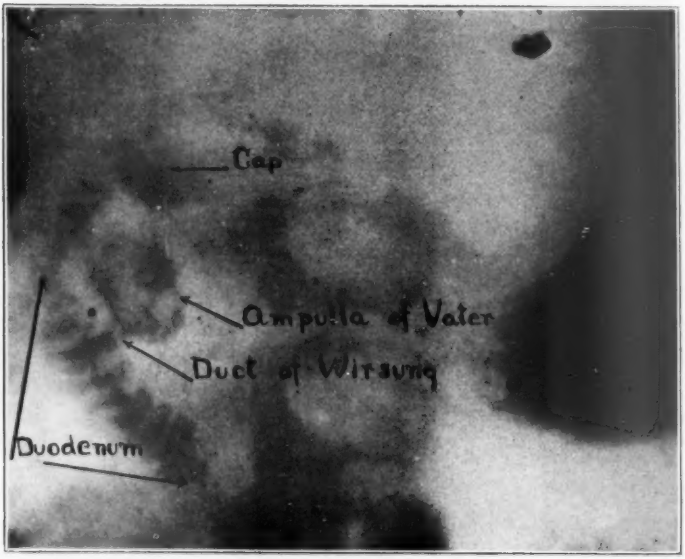

FIG. 12.—Distention of duct of Wirsung and ampulla of Vater by bismuth ingesta.

weaker chyme from the stomach or neutralized by alkaline solutions administered for this purpose an excess of acid must result. Is it not likely, therefore, that a prolongation of this condition will destroy the muscular coat, particularly if the mucosa has been bruised or broken by solid particles of food or by instrumentation? If this supposition be correct, any condition which diminishes, paralyzes, or inhibits duodenojejunal peristalsis will be a predisposing cause of postpyloric ulcer.

It is also important to note the far-reaching results of dilatation of the descending and horizontal duodenum, which may be filled by an active gastric peristalsis and not evacuated for a long time in consequence of the inhibition of duodenal peristalsis. The overdistended lumen offers no resistance to the expulsion of chyme through the duct of Wirsung into the ampulla of Vater (Fig. 12), and perhaps even into the common or cystic duct. This indicates a direct source of gall-bladder infection.[6]

Iliac Dilatation a Cause of Inhibition of Duodenal Peristalsis. Iliac stasis has been the all-absorbing problem of late among clinicians and surgeons interested in gastro-intestinal lesions. Although roentgenological evidence has played an important role in the diagnosis of this condition, interpretation of the findings has been influenced in many instances by the preconceived theory which the surgeon or practitioner was trying to prove. Case's roentgenological studies of the ileocecal region are an exception to this rather general rule.[7]

Careful observation of the entire gastro-intestinal tract at different periods after ingestion has shown that the inhibition of duodenal peristalsis during the later stages of digestion is usually associated with a distention or dilatation of the terminal portion of the ileum. It has been noted that as the chyme accumulates in and distends the ileum, duodenal peristalsis diminishes. The replete ileum, no longer a hungry gut, apparently exerts its influence to prevent overfilling by cutting off the supply from above. The connecting link between the gastroduodenal and ileocecal regions may be a chemical reflex. I suspect that when the ileum becomes replete it curtails through a reflex the amount of bile and pancreatic secretions, so that the alkalinity of the duodenal juices is not sufficiently strong to neutralize the acid or hyperacid chyme expelled from the stomach and rendered more acid by the secretions of the cap. Hence there ensues a cessation of the alternating alkaline and acid reactions of the descending duodenum, the exciting cause for the propulsive duodenal peristalsis, which normally evacuates

[6] A like duodenal dilatation may also be caused by an organic obstruction at the duodenojejunal junction, by pressure from the mesentery vessels, or by adhesions.

[7] Case, X-ray Observations on Colonic Peristalsis and Antiperistalsis, with Special Reference to the Function of the Ileocolic Valve, Read before International Congress, London, August, 1913; X-ray Studies of the Ileocecal Region and the Appendix, Amer. Quart. of Roent., November, 1912, p. 77.

the cap and propels the food through the duodenum and jejunum.[5] This theory presupposes some such chemical influence as the reflex described by Cannon, Marbeau, and Mehring, except that it controls the propulsive duodenal persistalsis instead of the pyloric sphincter. I have observed time and time again that if, after the contents of the stomach and cap have remained stationery for some time, the ileum be partly evacuated a rehabilitation of duodenal peristalsis will be established forthwith and food may be seen leaving the cap and passing forward through the jejunum.

When gastric achylia exists it may be that this reflex is materially altered, as the chyme is neutral or only slightly acid, and can be rendered alkaline by the duodenal secretions with great rapidity. This would account for the rapid evacuation of the stomach in some cases of gastric cancer.

Having demonstrated that gastroduodenal retention may be caused by the inhibition of duodenal peristalsis, and having associated this inhibition with a surfeited ileum, one next seeks to discover why the ileum does not rid itself of an oversupply by passing it forward into the cecum.

Roentgenological evidence indicates that iliac stasis or rather iliac dilatation may be caused by

1. Incomplete evacuation or fecal impaction in the cecum and ascending colon.
2. Various types of membranes and veils involving the colon and terminal cecum.
3. Kinks of the terminal portion of the ileum.
4. Insufficiency of the ileocecal valve.
5. Chronic appendicitis (primary or secondarily from adhesions, either before or after its removal).

All of these conditions may be recognized and differentiated from each other with a remarkable degree of accuracy by a thorough roentgenological examination, preferably in conjunction with a serial roentgenographical examination of the stomach and duodenum.

The symptoms of iliac stasis are rather varied because sometimes the symptoms of the cause prevail, and sometimes the symptoms of the effect prevail, particularly those referable to the stomach and cap. These symptoms will be considered under the discussion of each cause.

COLONIC STASIS. Colonic stasis is perhaps the most common cause of iliac stasis. Since the time when man dispensed with forefeet and assumed the erect posture it has been up-hill work for the ascending colon to evacuate itself. Overdistention of the cecum and ascending colon constitutes a large proportion of colonic

[5] If I have delved further into the causes of these roentgenological findings than my experience as a physiologist will justify, perhaps my suppositions may stimulate some physiologist to prove or disprove these theories.

stasis. The dilatation and atony of this region is partly compensated for by the active peristalsis of the terminal portion of the ileum. In proof of this, bismuth impregnated feces will be observed in the cecum much longer after a bismuth meal followed by a period of fasting than after a bismuth meal followed by the ingestion of food or possibly water. If the stasis (or constipation) in the ascending colon is persistent, unusual energy is demanded from the peristalsis of the terminal ileum. When its strength is not sufficient to break the blockade, delayed evacuation results, accompanied by a chain of symptoms, perhaps referable directly

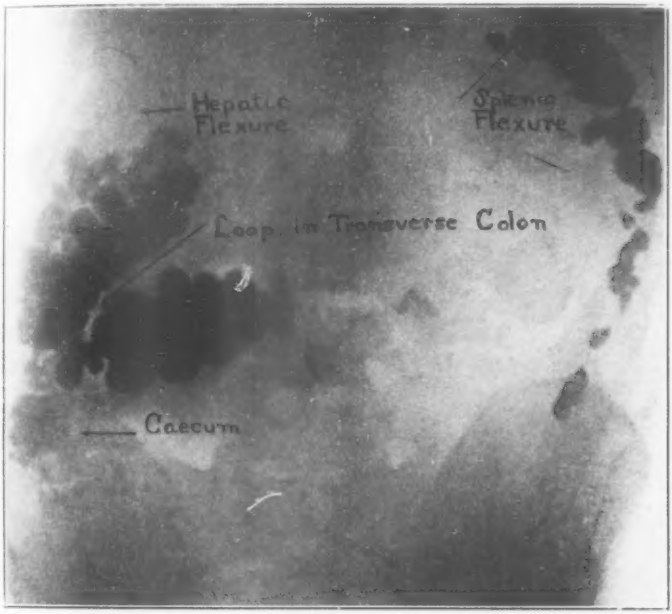

FIG. 13.—Stasis in cecum seventy-eight hours after ingestion.

to the exciting cause, "cecal constipation," or perhaps referred to the stomach and cap, as suggested earlier in this article. To overcome this obstruction, bismuth impregnated chyme may be seen frequently, forcing its way up through the fecal accumulations in the cecum and ascending colon, or the next meal succeeding the bismuth meal may be observed working up through the ascending colon (Fig. 13). If in such cases the cecum and ascending colon can be evacuated by properly applied manipulation, massage or even catharsis, previous to the ingestion of more food, stasis of food in the terminal ileum will thus be diminished, and often

the gastric or duodenal symptoms referred to the right hypochondrium will be relieved. Moreover, lesions in this region of a much more serious character may perhaps be prevented.

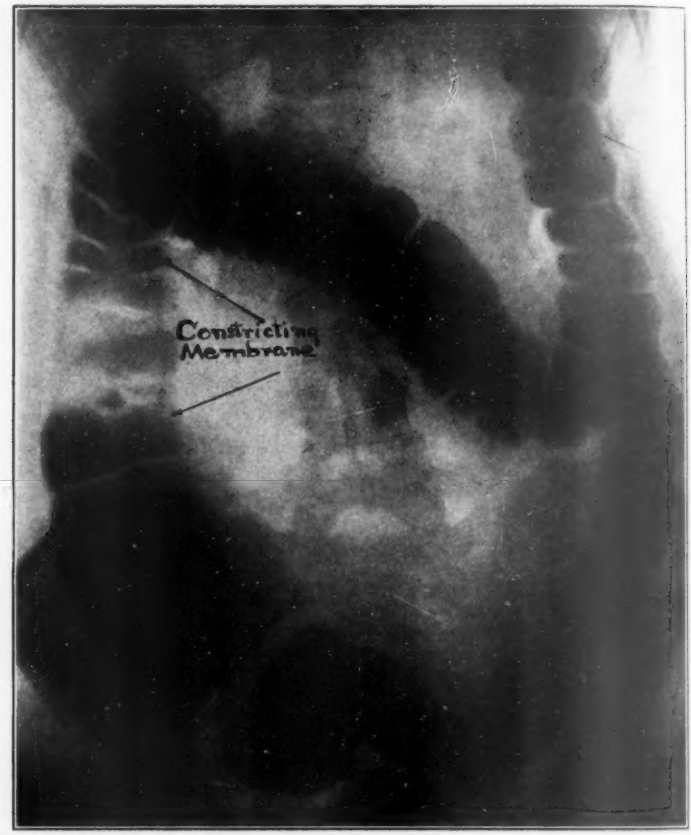

FIG. 14.—Pericolonic veil, involving ascending colon. Proved by operation.

MEMBRANES AND VEILS. The various types of veils and membranes involving the cecum, ascending, and first portion of the transverse colon undoubtedly cause an iliac stasis, either directly by affecting the colon or terminal ileum, or indirectly by the associated constipation which blocks iliac evacuation. These lesions may be diagnosed with a great degree of certainty by roentgenography, preferably combined with roentgenoscopy. The drawing up of the cecum, the irregular filling defects in the colon, and particularly the "double-barrel shotgun" appearance of the ascend-

ing and first portion of the transverse colon, referred to by George, are very characteristic roentgenological findings (Fig. 14). Such conditions are undoubtedly important factors in the cause of obscure symptoms referred to the stomach and cap, particularly those associated with hyperchlorhydria, and should be searched for when the right hypochondrium fails to reveal the seat of the trouble. Sometimes the direct symptoms of constipation are so severe that the presence of gastroduodenal symptoms is entirely overlooked.

I fear that the treatment of these conditions is not so simple as some surgeons would lead us to think. One group of surgeons will split these membranes, remove the veils, and watch the colon pop out of its cage, believing that the patient is freed from symptoms forever. Unfortunately they are likely to return, renewed by the conditions which originally caused them, or by the trauma of manipulation from surgical procedure. In other cases where there is atony and dilatation, some surgeons attempt to reduce the size of the colon and hold it in position by artificially producing the conditions which the aforementioned group of surgeons try to destroy. The most successful method of surgical treatment for such cases could be determined by postoperative roentgenological investigations in conjunction with careful clinical observations.

KINKS IN THE TERMINAL PORTION OF THE ILEUM. Kinks in the terminal portion of the ileum, either with or without mobile cecum, undoubtedly do occur and cause the group of symptoms described by Lane and recognized by others. But these kinks are a rare rather than frequent cause of iliac stasis. I was told by Dr. Jordan, who has made roentgenological examinations of many of Mr. Lane's cases, that the roentgenological finding on which he bases the diagnosis of kinks of the terminal portion of the ileum is immobility of this region to palpation under fluoroscopic examination, and that the presence or absence of iliac stasis is not so important a factor. On several occasions I have been able to recognize kinks of the terminal ileum with dilatation of the proximal ileum, and I have been able to demonstrate them to even the most skeptical observer (Figs. 15 and 16). When a kink really exists and causes iliac stasis and dilatation, especially if it is associated with symptoms surgery for its relief is undoubtedly indicated. The frequency with which symptoms of these lesions are referred to the stomach or duodenum, sometimes associated with organic lesions, viz., ulcers and adhesions, as described by Mr. Lane, should be strongly emphasized. But that iliac kinks and the associated group of symptoms and pathology occur with anything like the frequency that some observers would lead us to think, or that iliac stasis is caused solely or largely by kinks of the terminal portion of the ileum, is doubtful, as evidenced by the roentgenological findings. Therefore, operative procedure intended for the relief of kinks in

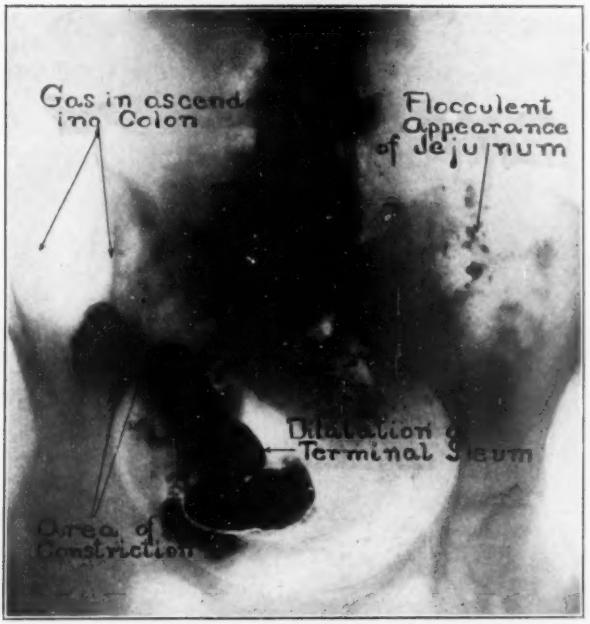

FIG. 15.—Lane's kink. Proved by operation.

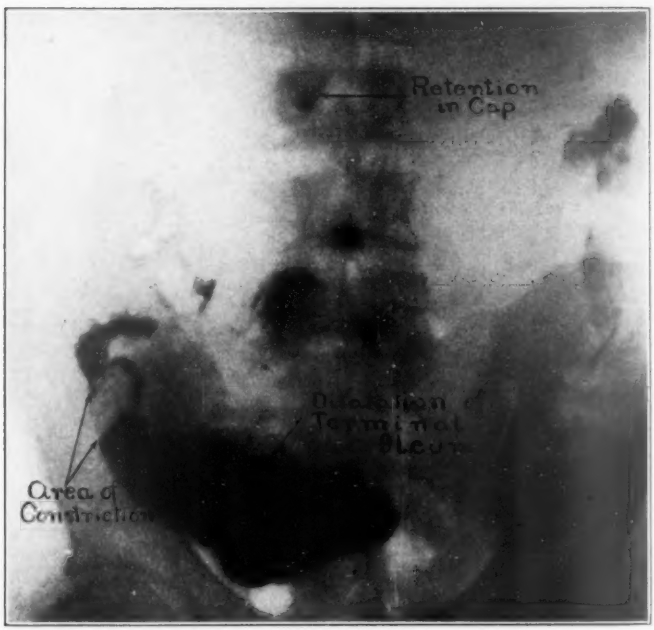

FIG. 16.—Lane's kink. Proved by operation.

the terminal portion of the ileum will not cure all cases of iliac stasis, nor relieve their associated symptoms. Furthermore, if the stasis is not caused by a kink, operative procedure may aggravate the symptoms.

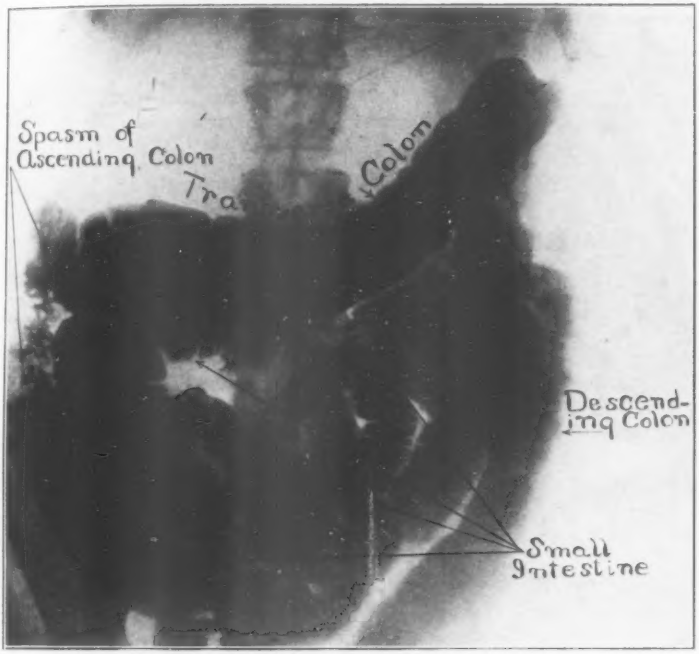

FIG. 17.—Distention of small intestine, caused by the passage of a bismuth clyster through an incompetent ileocecal valve.

INSUFFICIENCY OF THE ILEOCECAL VALVE. Insufficiency of the ileocecal valve is a condition which I first recognized in 1902 (Figs. 17 and 18). Out of the cases examined since that time I have observed about 200 cases of this irregularity, and have used every effort to arouse the interest of surgeons and practitioners in the subject without success. Even now in cases where the clysma passes all the way to the duodenum, and the patients present marked abdominal symptoms, surgeons and practitioners refuse to attribute any significance to this finding. I find that the only way I can interest them is to ask if they would expect symptoms if they fed their patients feces removed from the colon. I have failed to report this group of cases, at first because the question of tuberculosis occupied my attention, and later because my efforts were concentrated on gastroduodenal lesions. Kraus, Schwartz, Holz-

knecht, and more recently Groedel and Dietlan, have reported roentgenographical observations of ileocecal insufficiency. Case has published an article, and on several occasions demonstrated slides, showing the frequency with which this lesion manifests itself. Its clinical aspects have been described by Kellogg,[9] who has recently devised an operation for repairing an incompetent valve, and a method of constructing an artificial one, which will undoubtedly create a great interest in the whole subject.

FIG. 18.—Distention of small intestine, caused by the passage of a bismuth clyster through an incompetent ileocecal valve.

Some of my cases of ileocecal insufficiency, particularly the first ones that I recognized as such, where the bismuth had passed a long distance up the small intestine, were associated with periodical attacks of nausea, vomiting, fever, prostration and headache,

[9] Kellogg, Surgery of the Ileocecal Valve, Surg., Gyn., and Obst., November, 1913; Incompetency of Ileocecal Valve, Med. Record, New York, June 21, 1913.

and with cramping abdominal pain, especially marked in the right quadrant of the abdomen. This is the group of symptoms which has been attributed to a variety of causes, such as bilious attack, migraine, auto-intoxication, and frequently appendicitis. In some cases if the symptoms were sufficiently indefinite, the patient was permitted to retain his appendix, at least temporarily, in case it had not already been removed.

Reflecting on the roentgenological evidence, it occurred to me that this group of obscure symptoms was very likely due to the influx of large quantities of feces, loaded with bacteria and their products, from the colon, where they are normal, into the small intestine, which is relatively sterile compared with the colon. To increase my confidence in this theory, I found that the severity of the symptoms was proportionate to the length of the small intestine which the cecal contents traversed. Many cases were observed, presenting a mild degree of insufficiency, and the accompanying symptoms were only slight, or if acute, the attacks occurred at long intervals. Kellogg and Case have already referred to the iliac stasis, caused by or associated with this lesion, and my experience corroborates their observations.

The importance of ileocecal insufficiency justifies a communication limited to that subject alone, but it is impossible to consider it further in this communication, where it has been introduced merely as one of the potent factors in iliac stasis, and consequently in spasmodic and organic lesions of the stomach and cap.

Chronic Appendicitis. The roentgenological findings of chronic appendicitis are of immense diagnostic importance. The appendix, partially or completely filled, has occasionally been found by many roentgenologists, and reported at meetings or perhaps exhibited as a monstrosity. But Case and George deserve the credit of observing the appendix roentgenographically often enough to justify them in drawing conclusions as to the significance of its roentgenological appearance. Case states that the appendix may be shown in about 50 per cent. of the cases by milking the bismuth into its lumen. George maintains that he can show an appendix in eight cases out of ten, if it has not been removed. He finds that the appendix of a child is readily filled by manipulation, but so rapidly evacuated that it is difficult to roentgenograph it. It is doubtful if the mere filling of the appendix is of pathological significance. But as Case has already declared, much information may be derived by examining it roentgenographically. It is possible to determine its size, shape, and position, the presence or absence of areas of constriction or permanent kinks, and whether or not it is adherent to adjoining viscera. A persistent fleck of bismuth, remaining therein for several days, is an important finding, indicating incomplete evacuation. If this phenomenon is accompanied by spasmodic constriction of the cap or pars pylorica, and the

stomach, small intestine, and colon show no evidences of an organic lesion, there can be little doubt that the symptoms are due to chronic appendicitis. Even when the appendix is not visible to corroborate one's suspicions, the cause of the spasm may often be attributed to the appendix with considerable certainty, especially if the entire gastro-intestinal tract presents an otherwise perfectly normal appearance (Figs. 6 and 9).

DIAGNOSTIC VALUE OF ROENTGENOLOGY. It may be contended from a scientific stand-point that some of these deductions regarding the association of one lesion with another are not sufficiently proved. This may be true, but all inferences aside, the bare facts definitely shown by the roentgenological findings are sufficient to keep the scientific investigator busy for the next decade proving or disproving their association with each other. If our observations be correct, and we have a wealth of material to prove that they are correct, how vast is the field of functional gastro-intestinal disturbances thus opened up, whereon roentgenology is destined to throw the light which will reveal obscure lesions that have hitherto escaped detection by other methods of examination.

When the first alarm is sounded this search light should be put in action, lest, as Mayo warns, we deluge the alarm box and ignore the flames. If the roentgenologist is given an opportunity to make a complete examination, he can determine with a reasonable degree of certainty whether a torrent of surgical procedure is needed to extinguish the fire, or perhaps he may find that the chemical engine of hygiene, correct diet, and medication is sufficient. All of the lesions, with the exception of chronic appendicitis, may be diagnosed as accurately by a thorough roentgenological examination as by the old-fashioned exploratory laparotomy. Moreover, the roentgenological diagnosis can be made without loss of time or strength to the patient, and indicates whether medical or mechanical treatment will suffice or that surgical procedure is necessary.

REVIEWS

THE PROTEIN SPLIT PRODUCTS IN RELATION TO IMMUNITY AND DISEASE. By VICTOR C. VAUGHAN, M.D., LL.D., Dean of the Department of Medicine and Surgery of the University of Michigan; VICTOR C. VAUGHAN, JR., M.D., A.B., in charge of the Tuberculosis Work of the Detroit Board of Health, and J. WALTER VAUGHAN, M.D., A.B., Junior Attending Surgeon to Harper Hospital, Detroit. Pp. 476; 34 illustrations. Philadelphia and New York: Lea & Febiger, 1913.

THIS volume is a summary of the contributions of the Vaughans and their associates to the mechanism of disease. There are three distinct phases to this work:

First, the isolation of a common poisonous radical or "archon," common to all true proteins, of animal, vegetable, and bacterial origin, which they studied, This substance was not found in pure gelatin, which, it will be remembered, is a protein deficient in certain aromatic amino-acids, notably tyrosin. This poisonous deficient substance (or substances) is of unknown chemical composition, but the physiological effects produced by it in experimental animals suggest that it may be similar to or even identical with beta-imidazole-ethylamin (histamin or ergamin). Histamin may be obtained from histidin, one of the amino-acids constantly found in true proteins, by the removal of the carboxyl group. The poisonous archon, furthermore, seems to be closely related physiologically to the "anaphylatoxin" described more recently by Friedburger, and it may be synonymous with the so-called endotoxin of many bacteria. Friedburger's anaphylatoxin, the endotoxins of bacteria, and Vaughan's archon agree in one important particular: They appear to be poisonous and not toxins in the bacterial sense, that is, they do not stimulate antibody formation when they are injected into susceptible animals. True toxins stimulate antibody formation in susceptible animals under appropriate conditions.

Secondly, the effects of injecting the poisonous archon into experimental animals. Small amounts, 0.5 mg. approximately, injected intravenously kill guinea-pigs of average size within a very short time: the symptoms induced vary with the size of the dose. Fatal amounts induce symptoms essentially those described by various observers as acute anaphylactic shock, and the post-

mortem lesions are similar. The authors direct attention to the similarity of these symptoms with those following the injection of a homologous protein in a previously sensitized animal. They believe the same protein is concerned in either case.

Thirdly, the protein of the second injection in the sensitized animal is broken down *in vivo* by ferments which are elaborated by the tissue cells of the animal in response to the first injection of protein. This entire process is conceived by Vaughan to be one of parenteral digestion to free the tissues of the host from the alien protein. Among the products of the breakdown of protein in a sensitized animal is a substance resembling beta-imidazole-ethylamin. If this substance is liberated in a comparatively free state and in considerable amounts the animal dies acutely. If the protein is broken down in such a manner that this substance is liberated, combined to a greater or lesser extent with other substances, or liberated in very small amounts, the symptoms are correspondingly modified. Vaughan obtains this poisonous substance, which *in vivo* is produced by the action of specific intracellular ferments, by boiling protein with alcoholic caustic potash. According to Vaughan, therefore, the substance which he believes is closely related to beta-imidazole-ethylamin is the same as that produced in a sensitized animal following a second injection of protein and which causes acute anaphylactic death. The writers call attention to the effects of injecting protein parenterally at intervals frequent enough to prevent sensitization such injections very frequently result in the production of temperature curves and even lesions resembling strikingly those of certain of the well-known diseases, as, for example, typhoid.

These observations, and they are supported by a great deal of experimental evidence, have led to the Vaughan theory of the mechanism of disease, particularly that of bacterial causation. According to this theory, bacteria (alien protein) which develop in the tissues of the host lead to the formation of a specific ferment which will break down the protein of the bacterial bodies. During the interval which elapses between the first appearance of the bacteria in the tissues and the maturation of this ferment no clinical symptoms are apparent. This is the incubation period of the disease. When the ferment is mature it acts upon the bodies of the bacteria which are in the tissues, digests them parenterally, and liberates in greater or lesser amounts the poisonous archon. The parenteral liberation of this poison is, according to Vaughan, the factor which determines the clinical symptoms of the disease and to a very considerable extent the nature of the pathological lesions. The authors state dogmatically that the clinical and pathological manifestations of disease are attributable to the parenteral breakdown of protein (bacteria) in the tissues of the host. The nature and extent of this development and its location in the body

determine the clinical course and pathological lesions of the disease. The incubation period of a microbic disease, therefore, is that time which elapses between the initial development of the invading organism in the tissues of the host and the time required for the host to perfect a specific ferment, or perhaps ferments, to break down this alien protein. This brings the mechanism of disease into a distinct relationship with hypersensitiveness of anaphylaxis.

This work is unique and important. It places the mechanism of disease upon a chemical basis. There are two features of the theory, however, which require amplification:

First, it is rather difficult to conceive of ferment activity proceding rapidly enough *in vivo* to effect the cleavage of the protein molecule necessary to liberate this archon is sufficient amounts within the few minutes which elapse between the injection of protein in the sensitized animal and its death from acute anaphylactic shock.

Secondly, it is not clear how the rapidly fatal septicemias in which death may occur within eighteen hours of the initial infection can be explained upon this theory.

These objections may be purely academic, however, as Vaughan has stated very definitely that much remains to be done before the entire mechanism of disease is finally elucidated. The discussion of the experimental details and the exposition of the theory which is based upon this experimental work is very clear and very direct, and this work marks an important advance in medical science.

A. I. K.

Modern Medicine: Its Theory and Practice. In Original Contributions by American and Foreign Authors. Edited by Sir William Osler, Bart., M.D., F.R.S., Regius Professor of Medicine in Oxford University, England; Honorary Professor of Medicine in Johns Hopkins University, Baltimore; formerly Professor of Clinical Medicine in the University of Pennsylvania, Philadelphia, and in McGill University, Montreal; and Thomas McCrae, M.D., Professor of Medicine in the Jefferson Medical College, Philadelphia; Fellow of the Royal College of Physicians, London; formerly Associate Professor of Medicine in Johns Hopkins University, Baltimore. In five octavo volumes. Second edition. Vol. I: Pp. 1093; 43 engravings and 33 plates. Vol. II: Pp. 1144; 56 engravings and 20 plates. Philadelphia and New York: Lea & Febiger, 1914.

To those who had the opportunity of observing the widespread enthusiasm and approval that was accorded the first edition of Osler's *Modern Medicine* it will occasion no surprise to learn that less than four years after the last volume of the first edition was

published the first volumes of the new second edition have begun to appear. That the entire edition of a great system of medicine in seven volumes should be so rapidly exhausted is a more eloquent tribute to the value and success of the work than any approbation which the pen of a reviewer can ever hope to bestow.

The new edition, of which two volumes have recently been issued, is new in fact as well as in name. Under the able supervision of Sir William Osler and Thomas McCrae, so much rearrangement, revision, and alteration has taken place that the new volumes deserve careful consideration and review. In the preface the editors announce that in the new edition the number of volumes is to be reduced from seven to five. This reduction has been accomplished by increasing the size of the page, augmenting the number of pages in each volume, and by omitting the introductory chapters and historical sections that appeared in the first edition, together with certain articles on subjects that have undergone little or no change during the past few years.

A comparison of the original edition with Volumes I and II of the new edition, shows that radical changes have been made in their contents and arrangement. The new Volume I is devoted to bacterial diseases, infectious diseases of unknown origin, non-bacterial fungus infections, and the mycoses. This virtually was the contents of Volume II and part of Volume III of the first edition. On the other hand, the second volume of the new edition takes up protozoan and metazoan infections, diseases due to physical agents, intoxicants, diseases of metabolism, and constitutional diseases, all of which were discussed in the first volume of the older work; but besides this the new Volume II also includes the section on diseases of the respiratory system, which occupied half of the third volume of the first edition. In short, the range of subjects considered in the first two volumes of the new edition is practically the same as was contained in the first three volumes of the original edition.

To attempt a detailed discussion of the entire contents of these volumes is perhaps unnecessary in view of the fact that the various articles are contributed by practically the same eminent group of collaborators whose names appeared in the earlier edition. Certain features in the new volume are, however, worthy of mention.

In Volume I, Hektoen's admirable article of introduction to the study of infectious diseases furnishes an excellent review of the present-day beliefs on infection and immunity. Typhoid fever is discussed by McCrae in a single chapter almost fifty pages shorter than was his original contribution of five chapters. Such condensation is typical of the new edition, and for the most part has been accomplished by shortening the etiological and pathological considerations. The original articles on lobar pneumonia were written by the late John H. Musser and George W. Norris,

whereas the present contribution is more condensed, and is by Norris alone. Three chapters are devoted to tuberculosis. Its history and etiology are discussed by Baldwin, the pathology of tuberculosis by MacCallum, while the clinical aspects of the disease are taken up by Lawrason Brown. In the earlier edition five chapters were devoted to this subject. The new article on toxemia, septicemia, and pyemia is written by R. M. Pearce and J. Harold Austin instead of by the former alone. The chapter on Malta fever, by Sir David Bruce, has been thoroughly revised by George C. Low. In this new volume smallpox, vaccination, chickenpox, scarlet fever, measles, typhus, yellow fever, etc., are grouped respectively under diseases of doubtful or unknown etiology. Councilmann's contributions on smallpox and chickenpox have been revised by E. J. G. Beardsley, and McCollom in his article on scarlet fever has been assisted by Edwin H. Place. Thomas McCrae has revised the article on yellow fever written by the late James Carroll. In this new volume the well-known introductory chapter by Sir William Osler and Professor Adami's contribution on predisposition and immunity are omitted. In spite of this omission the new volume contains 156 pages more than did the first volume of the earlier edition.

In Volume II, under protozoan infections, the chapters by G. N. Calkins on protozoa and that by L. O. Howard on mosquitoes, which appeared in the older edition, have been omitted. The subject of trypanosomiasis by Sir David Bruce has been thoroughly revised by George C. Low. The chapter on relapsing fevers, originally furnished by McCrae, has been entirely rewritten by J. Y. Todd. The chapters written by D. L. Edsall on diseases due to the various mineral and other forms of chemical poisoning have been somewhat altered and revised by Normal B. Gwyn. The section on beriberi has been largely rewritten and an entirely new chapter on pellagra added by K. Heberden Beall. Under metabolic diseases P. B. Hawk's article on general considerations of metabolism replaces the one by Chittenden and Mendel. The entire section on metabolic disorders has been revised and enlarged. The final section of Volume II deals with diseases of the respiratory system. The contributors to this group of articles are the same as in the first edition, with the exception that pneumothorax is discussed by Frederick T. Lord instead of by Walter B. James. This second volume is 316 pages larger than was the original Volume II.

Judged by these two volumes the new edition of Osler's *Modern Medicine* should prove even a more valuable and popular work than did the first edition. Thoroughly revised in every detail, printed in a larger, clearer type, and in fewer volumes, it is safe to predict that, like its predecessor, this edition is destined to occupy a foremost position among the great systems of medicine.

G. M. P.

DISEASES OF THE STOMACH, INCLUDING DIETETIC AND MEDICINAL TREATMENT. By GEORGE ROE LOCKWOOD, M.D., Professor of Clinical Medicine in the Columbia University; Attending Physician to Bellevue Hospital, New York. Pp. 624, with 126 engravings and 15 plates. Philadelphia and New York: Lea & Febiger, 1913.

THIS treatise on diseases of the stomach differs from many similar works in that it is based almost entirely upon the personal experience of the author, an experience unusually varied and extensive, embracing large groups of cases, both from hospital and private practice. The book is not chiefly a summary of other men's works and a critical review of their opinions, but is throughout an expression of Lockwood's convictions arrived at after much mature consideration and careful study of ample clinical material. This statement, however, must not be construed as implying that Lockwood has overlooked the work of others or has furnished a one-sided discussion of the subject, on the contrary, he has freely availed himself of many important statistical studies, authoritative case reports, and noteworthy pathological and experimental observations. Indeed, when the author's conclusions and the results of his experience are at variance with those of other gastro-enterologists, Lockwood shows no narrow-minded dogmatism, but frankly sets forth all opposing opinions and gives a fair and impartial discussion of the controverted subject.

Lockwood has limited his book strictly to gastric disorders, and has avoided any systematic discussion of the intestines or the accessory organs of digestion. Nevertheless, he has not lost sight of the important relationship that exists between various gastric conditions and disease of the appendix, intestines, biliary tract, circulatory and nervous systems, etc. In fact, his final chapter is devoted particularly to a consideration of this phase of the subject. He follows the best recognized pathological and clinical classifications in his divisions of the subject. He first takes up the acute inflammatory conditions of the stomach. The discussion of chronic gastritis in its various forms which follows is an unusually clear and satisfactory account of conditions which too frequently are inadequately described. In the chapter on acute and chronic ulcer and on carcinoma and other tumors of the stomach, Lockwood has taken into consideration the best present-day views of both surgeons and internists. It is gratifying to find in a book so largely medical, a chapter devoted to acute dilatation of the stomach, a subject that at one time seemed preempted by the surgeons. Pyloric stenosis, both congenital and acquired, is entered into with extreme care. Diaphragmatic hernia, eventration, and volvulus are accorded unusually detailed consideration. The chapter on gastroptosis is a temperate and

rational presentation of a subject about which much unsubstantiated speculation and many radical opinions have often been expressed. Hyperacidity and achylia are dealt with at length and on the whole satisfactorily. The chapter on the so-called gastric neuroses, is an admirable commentary on the advances which have occurred in medical diagnosis during recent years. Whereas in older books much space was devoted to nervous affections of the stomach, Lockwood dismisses the entire subject in twenty-nine pages, in the course of which he emphatically warns that the group of nervous diseases of the stomach is a diminishing one and that the diagnosis is frequently unjustifiable and always dangerous.

Not the least useful feature of the book is the careful consideration given to treatment which is presented in detail and in a way that should prove of decided practical value. The importance of skiagraphy in gastric diagnosis is emphasized by the liberal number of excellent pictures of *x*-ray plates that suitably illustrate portions of the text.

Typographical errors are few, but they crop out here and there. For example, in the contents under Chapter X, "anatomy" should evidently be atony; again on page 190, line 15, "perforated" should be performed.

Lockwood's book is a well-balanced, interesting, and scientific account of diseases of the stomach, and should prove of great help to all who are confronted with the many perplexing problems in diagnosis and treatment presented by gastric conditions.

G. M. P.

PRINCIPLES OF SURGERY. By W. A. BRYAN, A.M., M.D., Professor of Surgery and Clinical Surgery at Vanderbilt University, Nashville, Tennessee. Pp. 677; 224 illustrations. Philadelphia and London: W. B. Saunders Company, 1913.

THIS is a small volume, which might have been made still smaller by proper condensation. It includes much more than fundamental principles, and as a consequence these very principles are not presented with sufficiently dogmatic terseness. Principles are the beginnings of things, or the elements of knowledge; among the older writers a favorite title for such a book as this is supposed to be was Institutes of Surgery. Certain laws apply to disease processes in general: laws of etiology, laws of pathogenesis, and laws of treatment. It is these laws which one looks to find in such a volume; but in the present volume it is difficult to find them. One might almost say that it appears uncertain whether the author has any conception of what the principles of surgery actually are.

The volume opens with a chapter of thirty pages on surgical

bacteria; but from the account given it does not appear that surgical bacteria are very different from medical or gynecological or genito-urinary bacteria, or from any bacteria about which the student learns in his course on bacteriology. The second chapter is on asepsis and antisepsis, and the third is on the process of healing. Not until the fourth chapter, and the ninetieth page is reached, is the student introduced to the first fundamental process in surgery, namely, inflammation. Inflammation in its broadest sense is the only pathological process except the growth of tumors in which surgeons have much interest; the healing of wounds, of abscesses, of ulcers, and of fractures is an inflammatory process; all surgical infections are inflammatory processes, whether caused by "pyogenic" bacteria, by bacilli of tuberculosis, by spirochetæ of syphilis or any other microbe. It seems logical therefore, to study this process before one studies its treatment; and antisepsis and asepsis are in their principles nothing else than methods of preventing and treating inflammation. It is true that the student is supposed already to have learned the pathology of inflammation in the course of his pathological studies, and that, strictly speaking, perhaps it is no more the business of a professor of surgery to teach inflammation than it is for him to teach bacteriology; but it is expedient for him to do so because in the pathological department so much stress is laid on morbid anatomy that the student overlooks the importance of pathogenesis. It is pathogenesis, *pathogenesis*, PATHOGENESIS, the course of the morbid process and *not* its appearance at any fixed stage that it is so important for the student to learn; but here again the volume now before us is lamentably weak. The pathological portions are little more than transcripts of morbid anatomy, with an occasional (an all too occasional) clinical application.

To conclude: the book is ill-balanced, not too well arranged, and though it contains much valuable information scattered throughout its pages, it also contains much matter that it is a waste of time to read, and which it was clearly a waste of time to write. It is not sufficiently dogmatic; it is a good deal too diffuse; and in few or no branches of surgery are the fundamental principles taught. For instance, in the chapter on hemorrhage the methods of applying ligatures are described (this belongs to the *practice* of surgery), but the laws (unchanged now for many years) which govern the surgeon in deciding the time, the place, and the manner of applying his ligatures are nowhere given; and in the chapter on wounds, though the method of tying sutures is described (again a point in the practice of surgery), no student will learn from this volume when to use interrupted and when continuous sutures, nor when to employ mass sutures or when to close his wound in layers.

Candidly speaking, we doubt whether this book will prove of much value to those for whose use it is designed. A. P. C. A.

SURGERY: ITS PRINCIPLES AND PRACTICE. FOR STUDENTS AND PRACTITIONERS. By ASTLEY PASTON COOPER ASHHURST, A.B., M.D., F.A.C.S., Instructor in Surgery in the University of Pennsylvania; Associate Surgeon to the Episcopal Hospital; Assistant Surgeon to the Philadelphia Orthopedic Hospital and Infirmary for Nervous Diseases. Pp. 1141, with 7 colored plates and 1032 illustrations, mostly original, in the text. Philadelphia and New York: Lea & Febiger, 1914.

ASHHURST, in a single volume of 1141 pages, has very successfully condensed for the students' purpose the principles underlying the subject of surgery. In his preface he states that the book is written to furnish a foundation upon which a knowledge of surgery may be built. Throughout the book consistently conforms to this idea. While many of the descriptions are brief, they at least call attention to the existence of the surgical lesion in question and outline its treatment—all that could be expected of a volume of such limited scope.

The book is divided into three general headings: (1) General surgery, which is discussed in nine chapters; (2) systemic surgery, discussed in seven chapters, and (3) regional surgery, in thirteen chapters.

The colored plates and 1032 illustrations have all been selected most wisely, to illustrate certain definite types of surgical lesion or their treatment.

The first four chapters are devoted to surgical pathology, with clinical descriptions and therapeusis sufficient to supplement such pathological knowledge as the student may have, and are commendably sufficient for all practical purposes.

Chapter V is devoted to surgical technique, minor surgery, and anesthesia, and is a model of condensation.

Exception should be taken to the use of carbolic acid as a means either of skin antisepsis or in preparation of the hands, because of the dangers underlying its use and its insufficiency of action. Under the subject of skin preparation Ashhurst does not enumerate enough of the present-day methods to give an entirely satisfactory idea of the standard methods now in use.

Under the subject of aspiration it would also seem wise to have discarded the antiquated method of aspiration by the preparation of a vacuum by the suction pump, and to have substituted in its place the alcohol method of Connell and the aspiration by means of the modified Sprengle pump (Kenyon and Poole).

The portion devoted to local anesthesia is incomplete, in that no mention is made of novocain for infiltration anesthesia or tropococain in spinal anesthesia.

Chapters VI, VII, VIII, and IX are devoted to the various forms of traumatism and are sufficiently comprehensive to meet the needs for which the book is written.

Systemic surgery, *i. e.*, surgery of the blood-vascular system, bones, joints, etc., is discussed in seven chapters.

The chapter devoted to fractures is especially commendable, although it would seem wiser to have introduced a description of the moulded plaster splints of Stimson.

The chapter devoted to the diseases of bones and joints are sufficiently complete, and consist of a readable and well-classified mass of surgical data.

The chapter on orthopedic surgery is a commendable addition to a work on surgery.

The remaining chapters, XVII to XXIX inclusive, deal with the subject of regional surgery.

Chapters XVII and XVIII deal with the head and spine, and are excellent. Chapter XIX gives sufficient of the surgery of the face, mouth, and neck, and is specially well illustrated by appropriately chosen illustrations.

The surgery of the breast, chest wall, lungs, hernia of the abdomen, the gastro-intestinal tract, and the gall-bladder, liver, pancreas, and spleen are handled in a very thorough and readable manner in the succeeding chapters, and conform to the modern opinions existing concerning these regions.

It might have been wiser to have placed the chapter on venereal diseases, the surgery of the male genital organs, and the surgery of the urethra and prostate before the surgery of the bladder and kidneys, and to have included some description of the modern use of neosalvarsan in the treatment of syphilis.

The final chapter on the surgery of the female genital organs is scarcely sufficient to meet the needs of the modern student. As far as the subject is discussed it is admirably handled.

Taken as a whole the book presents a readable, accurate condensation of the subject of modern surgery, and should find a ready field of usefulness as a text-book for the student and as a handy reference-book for the general practitioner. J. M. H.

Development and Anatomy of the Nasal Accessory Sinuses. By Warren B. Davis, M.D.

This work is based on 290 lateral nasal walls, the material being obtained partly from the postmortem room of the Friedrichshain Krankenhaus, Berlin, from the Daniel Baugh Institute of Anatomy of Philadelphia, and the gynecological and obstetrical departments of Jefferson Medical College of Philadelphia. The first two chapters are devoted to the method used in preparing and obtaining the specimens and the kind of anatomical material

used. The sinuses are taken up *seriatum*, and great stress is laid upon their embryology.

There is nothing new added to what is already known concerning the anatomy of the parts, though the early development of some of the sinuses in fetal life is a distinct advance over older embryological teachings.

The 57 illustrations by Dorothy Peters are excellent in detail, being taken from the original dissections, the majority being natural size unless otherwise mentioned. B. D. P.

DISEASES OF WOMEN. By CHARLES A. L. REED, A.M., F.C.S., M.D., Professor in the University of Cincinnati; Gynecological Surgeon to the Cincinnati Hospital, the German Deaconess' Hospital, and the Jewish Hospital; former President of the American Medical Association; author of *Text-book of Gynecology*. Pp. 944; 448 illustrations. New York and London: D. Appleton & Company, 1913.

THIS volume is written, as stated in the preface, "exclusively to meet the demands of utility." And while the author endeavors by his descriptions to place the knife in the hand of the reader and direct him through the operation, he wisely cautions against the assumption of surgical skill by the book-made amateur and endorses the present movement to limit surgical practice. One feels, perhaps, that medical and hygienic measures are submerged in a descriptive maze of over two hundred operative procedures. In recognition of the wide domain of gynecology, sections are devoted to diseases of the rectum, kidney, breast, and to the surgical conditions of pregnancy and parturition. Malformations, injuries, displacements, and foreign bodies are taken up in order. The various bacterial infections receive due attention. In the treatment of streptococcic infection of the puerperal uterus, a moot point, active surgical intervention, curettage, is recommended. Emphasis is laid on the necessity of early diagnosis of malignancy, and the hysterectomy of Wertheim is regarded by the author, notwithstanding its high immediate mortality, as offering best ultimate results in carcinoma of the uterus. Radium therapy of neoplasms is not mentioned, and the use of the *x*-rays in treatment is dismissed in a few lines. The section on menstruation, reprinted from a former work, shows little evidence of revision. The illustrations, mostly diagrammatic, are suitably chosen to correlate the text. The index is unusually comprehensive. The volume forms a welcome addition to the literature of the subject.

P. F. W.

A History of Laryngology and Rhinology. By Jonathan Wright, M.D., Director of the Department of Laboratories, New York Post-Graduate Medical School and Hospital. Second edition, revised and enlarged. Pp. 357; 13 illustrations. Philadelphia and New York: Lea & Febiger, 1914.

Dr. Jonathan Wright needs no introduction to any one practising the specialty of laryngology, and this book should be as well known as his earlier writings. The text of the first edition appeared in the *Laryngoscope*, but this has been greatly added to and brought up to date in the second edition. Fully half of the work is taken up with the history of the specialty from the most remote times of which we have medical records to the beginning of the last century. Much that is of interest to the student can be gleaned from these pages—interest chiefly of an historical nature. In the last half of the book, which is devoted to the development of the specialty of laryngology and rhinology as now practised, every new phase of the subject is taken up in detail and in chronological order and developed to its present status. To one interested in the history of different procedures and the question of priority in the discovery of new remedies, modes of treatment, and operation it is invaluable, as every author of note is quoted and the book thus becomes an index-medicus and a bibliography of great use to one who is engaged in literary effort. A double index of subjects and of personal names, with the bibliography of all references at the bottom of each page, immeasurably increases its value. G. M. C.

Medizinisch Chemisches Laboratormins Hilfsbuch. Von Dr. Med et Phil. Ludwig Pincdissohn. Pp. 443; 75 illustrations. Berlin: F. C. W. Vogel, 1913.

This work is intended to serve as a laboratory manual for medical men engaged in medical chemistry and, secondly, as a convenient reference book for more experienced physiological chemical workers. A considerable variety of subjects receive brief treatment, viz., general chemical and analytical methods, the usual examinations or urine, feces, blood, etc., some of the more difficult physiological chemical procedures even the ferments and bacteriology being touched on.

Appended are a considerable number of tables of chemical, physiologico-chemical, and more general import.

This book is to be ranked in with a number of others of the same general character and seems scarcely to show any marked advantages over many already printed. N. W. J.

PROGRESS

OF

MEDICAL SCIENCE

MEDICINE

UNDER THE CHARGE OF

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Abderhalden's Test in Epilepsy.—LERI and VURPAS (*Bull. et mém. de la soc. méd. des hôp. de Paris*, 1914, xxix, 964) raise two questions: (1) Does dysfunction of an organ necessarily cause the appearance of specific ferments in the blood, and (2), does the finding of a ferment capable of breaking down a certain tissue necessarily imply dysfunction of that particular organ? On the basis of numerous negative reactions Leri and Vurpas are inclined to give a positive "no" for answer to the first, but to the more significant second question, the study of some 50 cases failed to yield a positive answer. For instance, 25 cases of pure epilepsy yielded sera capable of breaking down brain tissue, while 10 others equally clear-cut failed to do so, results quite in harmony with those secured by Binswanger. Leri and Vurpas, however, differ from Binswanger in believing that the tissue destruction bears no constant relation to the attacks themselves, nor do they believe that sero-diagnosis will enable one to differentiate between constitutional and organic types of epilepsy. They find that the reaction is apparently not influenced by the number or severity of the attacks, the age of the patient, the age of onset or the duration of the disease. The most positive reactions took place in patients presenting outspoken mental deterioration. While Levi and Vurpas are unable to draw any valuable prognostic or therapeutic conclusions, they believe in the fundamental significance of Abderhalden's reaction.

Differential Counts of White Cells in the Counting-chamber.—DUNZELT (*Münch med. Woch.*, 1913, lx, p. 2816). Numerous attempts have been made to devise a suitable and accurate method for making

differential leukocyte counts by the use of the ordinary counting-chamber, thereby making the quantitative and qualitative study of the white cells essentially a single process. Dunzelt states that the method here described makes possible the ready recognition of all cells, normal and pathologic. Two stock solutions are required: (A) Methylene blue (Med. Hochst), 0.08 gm. dissolved in 50 c.c. of distilled water and filtered. (B) Eosin 4 B. Hochst 5 gm., acetone 30 c.c. and H_2O 100 c.c., filtered. To use one takes 20 c.c. of A and 40 c.c. of B: shake well and filter into a dark bottle in which the solution remains unchanged for several weeks. The ordinary blood pipettes are filled in the usual manner, the mixed solution being the diluent. Large mononuclears are readily distinguished by their size and weaker staining properties from lymphocytes which stain a deep blue. Of the granular cells, "mast cells" alone present some difficulties, often appearing, as with Ehrlich's stain, vacuolated. Nucleated red cells are easily recognized.

Complement Fixation in Gonorrhea.—Thomas and Ivy (*Arch. of Int. Med.*, 1914, xiii, 143). The report is based upon 240 cases of gonorrheal disease beside a number of cured cases, controls of a most varied type, acute and chronic urethritis, arthritis, and different types of ascending infections in women. A number of antigens were used, namely, a twenty-four-hour monovalent unfiltered antigen, trivalent and hexavalent filtered antigens, and a gonorrheal vaccine secured from Parke, Davis & Co. The first of these was made as follows: the twenty-four-hour growth on blood agar was washed off with distilled water, thoroughly shaken and allowed to autolyze for twenty-four hours at 37°, after which it was placed in a water bath at 60° for half an hour. For use it was diluted 1 to 10 with normal salt solution. Thomas and Ivy secured the following positive results: 9.9 per cent. in anterior and posterior urethritis; 21.5 per cent. in clinically cured cases; 66.2⅔ per cent. in cases of stricture; 87.5 per cent. in epididymitis; and 100 per cent. in cases of gonorrheal arthritis. Having never observed a positive test in a non-specific case, they are inclined to regard a positive fixation as a certain indication of the existence of gonorrhea. The test is of great value in the differential diagnosis of diseases of the female adnexa. It serves as a splendid index of the results of treatment, and in chronic cases particularly gives positive results much more frequently than do either microscopical or bacteriological methods.

Congenital Hemolytic Jaundice.—Chauffard (*Ann de méd.*, 1914, p. 3) cites instances to show that hereditary lues plays a distinct role in the etiology of congenital hemolytic jaundice. Thus in a man, aged fifty years, and his two daughters, all of whom had been jaundiced and anemic from birth, the Wassermann reaction was positive, and there occurred frequent attacks of pain in the region of the spleen, associated with an aggravation in the degree of the jaundice. The resistance of the red-blood cells varied from 0.64 to 0.62 per cent. NaCl. It is interesting that in 2 of the patients the injection of Salvarsan was followed by a further reduction in the resistance of the red cells and an increase in the anemia, jaundice, and hemolysins in the blood. These phenomena, regarded by the author as of the nature

of a Herxheimer reaction, were observed in another case of a man, aged twenty-two years, who also showed a positive Wassermann reaction. Latent tuberculosis also appears to have some bearing upon the disease. Thus in 3 cases that presented no symptoms, sharp reactions followed the injection of tuberculin, while in 1 case the spleen became doubled in size and the resistance of the red cells fell from 0.64 to 0.76 per cent., NaCl associated with the presence of many nucleated and granular cells in the circulating blood. Chauffard is inclined to regard hemolytic jaundice not as a disease entity but as a syndrome probably produced by numerous factors, of which hereditary syphilis and tuberculosis are at present best recognized.

Therapy in Graves' Disease.—Klose (*Berl. klin. Woch.*, 1914, x, 10). calls attention to the fact that while the involvement of the thymus in Basedow's disease has up to the present time served in many instances as a contra-indication for surgical procedure, today an entirely different point of view exists. It is probable that no case of Graves' disease exists without there being some involvement of the thymus at the same time, for Graves' disease is one of the entire branchial system. The degree to which either the thymus or the thyroid gland may be involved in the disease progress is a variable one, and in every case one must endeavor to decide which organ or gland in the system is the one concerned. Certainly in the majority of the cases the essential process in one of thyroid origin in which the thymus is only quantitatively affected and spontaneously recovers its normal condition, after reduction of the thyroid by operation. In a second group of cases, however, both the thyroid and the thymus are involved, and apparently in a specific sense, as seems to be shown by histological methods, though the glands themselves need not necessarily be enlarged. This type of thymus is the one most dangerous for the individual, particularly by reason of its chemical poisonous action upon the heart, especially during operations in the vicinity of the thymus, which may result in a mobilization of its toxic principle. In some of the severest cases of this type, Klose finds that the thyroid seems to be infiltrated with tissue of a thymus nature, so that he speaks of a "thymisation" of the thyroid gland. Experimentally it may be shown that such thymus glands are much more toxic for animals than are normal ones. There is yet a third group of cases in which the essential process is limited to the thymus, with practically no involvement of the thyroid. The type of thymus Basedow occurs quite infrequently, and histologically it may be shown that the thyroid is practically free from any specific changes. From a therapeutic point of view the same procedure is to be recommended in these thymus cases as is ordinarily used in the thyroid group—namely, the removal of some of the thymus itself. As yet it is somewhat difficult to diagnose clinically qualitative involvement of the thymus glands in cases of Graves' disease, but there are certain criteria which are of some help. These are a widening of the shadow in the *x*-ray picture of the mediastinum, the finding of myasthenia in testing the muscles with electricity and the special predominance of vagotonic symptoms in association with unusually high absolute values for the lymphocytes in the blood. Serodiagnosis by means of Abderhalden's reaction is also of great value. Absolute criteria for the

diagnosis of the specific involvement of the thymus are not yet available. Klose recommends that in all severe cases of Basedow's disease the thymus should be removed, as is done in the combined excision method at Rehn's clinic. In the last two years 200 operations have resulted in no fatal cases, and it has been striking to see the rapid improvement of the general condition of the patients and the very slight postoperative reactions which have occurred. The technique of the operation, which is easy, consists essentially in local anesthesia and removal of the thymus from its capsule, since removal with the capsule may lead to fatal hemorrhage.

Complement-fixation in Malaria.—GASBARRINI (*Zeit. f. Imm. u. exp. Therapie*, 1913, xx, 178-197). The application of the Bordet-Gengou phenomenon to the study and diagnosis of malaria has yielded some rather interesting results. The preparation of the antigen was as follows: blood was withdrawn from patients known to have abundant parasites in the circulating cells; this was well washed by centrifugalization, dried, and finally ground up into a powder. This powder finally is made up in a 1 to 30 suspension, incubated for several hours at body temperature, and the clear supernatent fluid, removed after centrifuging, is used in the test. It was found that no deviation of complement occurs when the serum is used taken during a chill or the febrile period of a malarial attack. If, however, the normal amboceptors of such sera are first removed through an adsorptive process, according to the method of Rossi and Mintz, complement-fixation occurs. It was also found that sera taken from chronic cases which had been free from attacks for varying lengths of time, gave more or less deviation of complement, even without previous adsorption. Numerous controls from normal and diseased cases gave consistently negative results.

A Case of Paroxysmal Hemaglobinuria.—WEIL and CHEVALLIER (*Bull. et mêm. de la soc. méd. des hôp. de Paris*, 1914, xxx, 35), presents a case which is unusual in that it showed two distinct types of onset. The first was the usual sudden type occurring immediately after and the result of the influence of cold. The second type, though similar in its manifestations, developed only after several days, during which there were numerous prodromal symptoms, such as, muscular pains colic-like attacks in the kidney region, and extremely severe headaches. A few hours before the actual onset marked meteorism occurred, and soon after actual commencement of the attack a severe chill took place, followed by immediate improvement coincident with the passage of the first hemoglobin-containing urine. The Wassermann reaction was positive. The same was true of the Donath-Landsteiner reaction after placing the arm in iced water. It was necessary, however, to use fairly large amounts of serum not diluted with physiological salt solution nor heated to 56° C. During the actual attack there was noticed a marked acceleration of the blood coagulation as well as a lymphocytosis as high as 40 per cent., though immediately prior to the onset the polynuclear neutrophils were absolutely increased. The case also showed a complete suppression of the urinary secretion for several hours prior to the chill, followed by a polyuria. The fact that a brother of the patient suffered from the same type of disease suggests strongly that it may be an hereditary one.

SURGERY

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Intrathoracic Surgery.—LAPEYRE (*Archiv. d. Chir.*, 1913, vii, 1909) reviews the status of present day intrathoracic surgery. The difficulties previously encountered in making an accurate diagnosis, which should precede operation, have been largely overcome by the *x*-ray, and the fear of dangerous pneumothorax by various methods of artificial respiration during the operation. It is important to regard total pneumothorax as a rapidly fatal condition. Artificial respiration is not absolutely necessary in all cases, for instance in operations on the anterior mediastinum, as in operations on the heart and for tuberculous lymph nodes. The operation field in a posterior mediastinotomy is so small and deep that it is best reached through the pleural cavity, so that artificial respiration is necessary in this operation. In operating on the pleural cavity, the presence or absence of adhesions is very important. If adhesions are present, artificial respiration is not necessary, but it is absolutely necessary if the pleura is normal. The Sauerbruch chamber and Brauer apparatus are costly and little employed. The method of Meltzer is much more simple and is sufficiently dependable. Lapeyre has tried to simplify this method by interrupting the current of air being sent into the lungs by the bellows used for artificial respiration in the physiological laboratory. This method was employed in animals in four large thoracotomies (circular suture of the esophagus, pericardiorrhaphy, resection of the pneumogastrics), without any disturbance being noted in the blood. He does not insist on this method but believes that with further development it can be of much value.

Post-traumatic Ossification in the Region of the Elbow-joint.—LEHMAN (*Deut. Zschr. f. Chir.*, 1914, cxxvi, 213) says that the elbow-joint, more than other joints, exhibits a predilection for post-traumatic ossification: To a certain extent this is due to its anatomical formation. These ossifications may be found after traumata of every kind, but are especially frequent after dislocations. The trauma is the determining factor. Etiologically, an individual predisposition must be assumed. The bone formation may take place from intramuscular connective tissue, as well as from the periosteum. There is practically no difference between the ossification of muscle origin and that of periosteal origin,

since both develop together. The neighboring soft tissues participate in the structure of the callus. Appropriate treatment of the recent injury is the best prophylaxis of the ossification. It involves rest and protection of the injured soft tissues, as far as possible, and the promotion of absorption. Vigorous massage and active movements are to be strictly avoided. For persistent thick infiltration, fibrolysin treatment is to be recommended. The completed ossification is capable of undergoing absorption, so that its treatment should be mostly conservative. An operation is indicated only in long continued, severe disturbances of function, and when there are complications from pressure on nerves and vessels. It should not be done before the conclusion of the process of ossification.

The Indications in Operations for Aneurysm and for Injury of the Bloodvessels.—COENEN (*Zentralbl. f. Chir.*, 1913, xl, 1913) says that whether one must treat traumatic aneurysms by ligature of the afferent and efferent branches with extirpation of the sac or by the employment of the vessel suture, and further, whether an injured large bloodvessel should be ligated or the vessel suture employed, depends on development of the collateral circulation. This should be determined before or at the time of the operation. From his experience with aneurysms in the first and second Balkan wars he developed the following method of testing the collateral circulation: Without interruption of the current the aneurysmal sac and the artery at each end are exposed. The artery is ligated above and below, close to the sac. Then below (on the peripheral side) the ligature a clamp is applied and the artery divided between this clamp and the peripheral ligature. If the clamp is now removed and bright red blood escapes from the open peripheral stump a sufficient collateral circulation is present, and one may safely apply the ligature (positive collateral sign). But if no blood escapes from the open peripheral stump, then it may be assumed, provided that a thrombus has not developed, that no collateral circulation has formed (negative collateral sign), and the vessel suture with implantation into the saphenous vein is indicated. The color of the toes or fingers help in determining the condition of the collateral circulation as well as the color of the blood which escapes from a puncture in the affected region. One cannot always wait for the stationary stage of the aneurysm nor for the complete fibrous encapsulation of the sac and formation of the collateral circulation. This is the case in war hospitals or when the escaping blood is progressively infiltrating the muscles and producing nerve paralyses. In such cases it may be necessary to operate and expose the vessels with the limb made bloodless by the Esmarch tourniquet. After clamping the vessel above and below the Esmarch band may be removed and the above test of the colateral circulation made. He operated on three stationary and four progressive aneurysms. In two, saphenous implantations were made. Gangrene did not occur in any.

Gastroduodenostomy for Ulcer.—BRUN (*Zentralbl. f. Chir.*, 1914, xli, 140) has been employing for a year gastroduodenostomy instead of gastrojejunostomy for florid pylorus and duodenal ulcer. He calls attention to the mobility of the duodenum and its availability in this

operation, but admits that, exceptionally, adhesions and inflammatory exudate will prevent the employment of the duodenum for the anastomosis. According to his experience a gastroduodenostomy for stenosis and ulcer can be performed easily much more frequently than is usually thought. He advises a vertical or, which is better, an oblique abdominal incision along the costal margin. The latter gives an excellent view of the field of operation. In simple cases with small ulcers in the anterior wall of the horizontal portion of the duodenum he usually employs a lateral gastroduodenostomy. The ulcer is turned inward by successive sutures until the afferent and efferent loops are brought together. This makes the performance of the gastroduodenostomy easier, since the stomach and mobilized, descending portion of the duodenum are already close together. Where a complete occlusion of the pylorus seems indicated, whether the ulcer is prepyloric or duodenal, he divides the stomach completely through, closes the duodenal end, and implants the gastric stump, as it is, end to end, into the descending portion of the duodenum. The anastomosis is made higher or lower according to the extent of the infiltration of the ulcer zone, or according to the desire to change the plane of the stomach. The blind closure of the peripheral lumen is safe, even when it involves the ominous duodenum, if one carefully respects its circulation. The new anastomosis removes the ulcer from the food current completely, permits the mobility, innervation, and chemistry to remain almost undisturbed, and respects the physiological principles.

Intrathoracic Goitre.—LAMSON (*Annals of Surgery*, 1914, lix, 191) reports two interesting cases of goitre extending downward into the thorax. In one a cyst developed at the lower pole. At the same time there was some enlargement of the thyroid gland in the cervical region, which about one and a half years ago disappeared, as the patient stated (probably during a fit of coughing it was drawn beneath the clavicle and was retained in the thoracic cavity). After that, beginning rather acutely, there was a marked increase in the severity of her symptoms, which were gradually growing worse. In the second case there was never any sign of any visible goitre, the growth having developed at the lower pole of the gland and extended downward into the mediastinum during the entire course of the growth, producing such marked narrowing of the trachea as to almost strangulate the patient. Both patients made a complete recovery after operation.

Hematuria in the Course of Different Forms of Appendicitis.—NOVE, JOSSERAND, AND FAYOL (*Jour. d'Urolog.*, 1914, v, 121) say that hematuria may occur in all forms of appendicitis, acute and chronic, and after appendectomy. In the acute form it appears at the cessation or after the general symptoms of appendicitis. It appears suddenly without premonitory signs. It is intermittent, of short duration, and is variable in quantity. In the chronic form it precedes the appendicular symptoms proper. It occurs in patients with long-continued and variable pain in the abdomen, gastralgia, with or without vomiting, constipation, meteorism, and pains in the right iliac fossa. It coexists with nephritic colic, confusing the diagnosis with renal or ureteral calculus, especially as lithiasis can coexist with appendicitis. Examina-

tion of the urine and cystoscopy are necessary for the diagnosis. Even *x*-rays may leave it in doubt. The hematuria is generally benign, without elevation of the temperature, or disturbance of the general condition, and ordinarily leaves no urinary sequelæ. Operation shows that frequently the appendix is in the posterior situation, adherent to the ureter and kinking it. This explains the obstruction of the ureter. In acute forms which come to autopsy an intense congestion of the kidney is found. Besides concomitant lesions of the urinary apparatus (lithiasis, tuberculosis) the hematuria can be due to general causes (nephritis) or to local causes, probably to reflex renal congestion in most cases. The appendix and ureter have a common innervation, the abdominal sympathetic. There is no treatment for the hematuria of appendicular origin in itself. It is often only a symptom of chronic appendicitis, which calls for appendectomy, after which it disappears. In the acute forms it is only a phenomenon which in itself is not an indication for operation. After appendectomy it is only a curious incident in the convalescence. In no cases do important renal lesions persist to become troublesome in the future.

Intracranial Injections for Trigeminal Neuralgia.—Hartel (*Deut. Zeitschr. f. Chir.*, 1914, cxxvi, 429) usually uses local anesthesia with novocain by Schleich's method for the alcohol injection of the Gasserian ganglion, infiltrating intra- and subcutaneously a line from the anterior border of the ascending ramus of the lower jaw to the nasolabial groove, on a level with the upper teeth. An assistant fixes the head of the patient. The guard on the cannula is placed 6 cm. from the point, and the finger feels in the mouth, with the jaws closed, for the space between the ascending ramus of the lower jaw and the tuberosity of the upper jaw. The cannula is passed through the cheek, under the mucosa, in this space, until it strikes the smooth under surface of the temporal bone. The finger is then removed from the mouth and the glove changed. The guard on the cannula being close to the skin, is withdrawn 1.5 cm., which is the depth to which it is to be passed into the skull. With the face of the physician directly opposite that of the patient the needle is so placed that a prolongation of it would strike the pupil of the same side. The point of the needle is made to feel its way backward carefully until it is in the same plane as the articular tuberosity of the malar bone. Pain will now develop from contact with the third division of the trigeminal nerve and its branches. After some manipulation the resistance disappears and the cannula passes over the round anterior margin of the foramen ovale into the cranial cavity. Härtel says that by repeated injections with alcohol the ganglion can be made permanently anesthetic. He has employed puncture through the foramen ovale for the treatment of neuralgia, local anesthesia in large operations on the face, alcohol injections in symptomatic neuralgia from malignant tumors, for diagnosis in meningitis, and the treatment of head tetanus by intracranial injections of antitoxin. The indications for the various methods of treatment of trigeminal neuralgia are as follows: Recent cases call for laxatives and Bier's hot-air apparatus, especially the hot-air steam massage. Peripheral or central injections are also good. Chronic cases, localized to one branch, should receive peripheral basal injections. Extensive

neuralgias and those recurring after peripheral operations should receive alcohol injections of the Gasserian ganglion, which should be repeated until permanent anesthesia is obtained. In those cases in which repeated intracranial injections give no help, and in such cases where the puncture of the foramen ovale is unsuccessful for anatomical reasons, resection of the ganglion is indicated. Secondary neuralgias are to be treated etiologically. Only when due to inoperable tumors is the alcohol injection to be thought of. Hysterical cases are to be excluded so far as possible.

THERAPEUTICS

UNDER THE CHARGE OF

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The Effect of Digitalis on the Blood Pressure and Pulse Pressure in the Presence of Cardiac Decompensation.—LAWRENCE (*Boston Med. and Surg. Jour.*, 1914, clxx, 37) writes concerning the effect of digitalis when administered to patients with cardiac decompensation from various causes. He records 26 cases in detail with the effects observed from digitalis which was administered in most of the cases in the form of digipuratum. From a study of these cases Lawrence gives figures that apparently indicate that in the presence of cardiac decompensation digitalis preparations cause, as a rule, a fall in blood pressure which is usually associated with an increased urinary output. An increased systolic pressure occurs in a small number of cases and is not associated with a diuresis. It appears to him, therefore, that conditions in which an increased systolic pressure might produce untoward results do not constitute "contraindications to the administration of digitalis if cardiac decompensation indicates its use. Such conditions include arteriosclerosis, angina pectoris, and nephritic hypertension. The effect of digitalis on the diastolic pressure is similar to that on the systolic, but changes in diastolic pressure are usually of less amplitude than those observed in systolic pressure. For this reason a fall in systolic pressure usually means a diminished pulse pressure. Such a diminished pulse pressure does not necessarily mean a decreased efficiency of the circulation if the ratio of pulse pressure to maximum pressure is increased. Indeed, such a change may coincide with the increased efficiency of the circulation, as is shown by the fact that in 81 per cent. of the cases showing a fall in blood pressure there occurred a diuresis. Lawrence concludes that the effects of various drugs on the blood pressure, as determined by experiments on animals, do not furnish reliable criteria for the administration of such drugs to man. The pressure-raising effect of digitalis noted in animals and in healthy individuals does not occur, as a rule, when the drug is administered to individuals suffering from cardiac decompensation.

Serotherapy in Scarlet Fever.—Koch (*Münch. med. Woch.*, 1913, lx, 2611) writes concerning the treatment of scarlet fever patients by injections of serum derived from the blood of convalescents from scarlet fever. A mixed serum from the blood of a number of scarlet fever convalescents, free from tuberculous or luetic disease is used preferably to a serum obtained from an individual case. In 1912, Reiss and Jungmann reported 12 cases of scarlet fever treated with good results by this method and Koch adds 28 more cases in this article. Of this series, 1 patient died, but this patient was practically moribund on admission to the hospital and died one hour after the first injection. The effects of the treatment were most striking in the severe toxic cases without complications. Koch gives temperature charts in his article that seem to show the prompt action of the serum treatment upon the temperature curve. He says that this effect was parallel with marked clinical improvement in the individual cases.

The Intrameningeal Treatment of Tabes Dorsalis and Cerebrospinal Syphilis.—Boggs and Snowden (*Jour. Amer. Med. Assoc.*, 1913, lxi, 2268) report concerning the treatment of tabes dorsalis and cerebrospinal syphilis by the intraspinal injection of serum removed one hour after the intravenous injection of salvarsan or neosalvarsan. The Swift and Ellis technique was followed, except that they injected larger doses of the undiluted serum. Blood was withdrawn one hour after the intravenous administration of salvarsan and allowed to clot. The next day the serum was removed, centrifugalized, and heated at 56° C. for half an hour. Lumbar puncture was then done, cerebrospinal fluid withdrawn, and exactly enough serum injected to replace the fluid. The amounts varied between 20 and 35 c.c., and the treatment was repeated from every ten to twenty days until the spinal fluid was normal in respect to the cell-count and Wassermann. In every case there was marked improvement, the cell-count dropping to normal and the Wassermann becoming less marked and in most of the cases entirely negative. The most constant result was the disappearance of the lightning pains and other sensory disturbances, and this resulted in a more cheerful mental attitude and a corresponding improvement in the appetite and nutrition. The effect on locomotion was slower in development and less marked, but definite, and in some cases great improvement was achieved, rather more pronounced, apparently, than in patients treated by smaller doses of diluted serum.

The Benzol Treatment of Leukemia.—Mühlmann (*Deutsch. med. Woch.*, 1913, xxxix, 2083) reports a case of lymphatic leukemia treated with benzol during a period of nearly six months with a final fatal result. This patient had received a total of 175 gm. of benzol during this time and at the autopsy extensive necrosis of the liver was found. The patient showed marked improvement after the first three or four weeks of benzol treatment and continued to improve for two weeks after the discontinuance of the remedy. This period of improvement was closely followed by a relapse which yielded to further benzol treatment, the leukocytes dropping from 60,000 to 20,000. This temporary improvement was followed by a severe relapse while on

the benzol and the patient rapidly failed. Pappenheim has found necrosis of the liver in rabbits after the administration of benzol for continued periods of time and Neumann has also reported necrosis of the liver in a case of myeloid leukemia treated with benzol. Mühlmann cautions against the continued use of benzol in view of this apparent destructive action of benzol upon the liver.

The Scientific Basis for Vaccine Therapy.—PEARCE (*Jour. Amer. Med. Assoc.*, 1913, lxi, 2115) says that prophylactic vaccination rests on a sound scientific basis of experimental study and clinical observation. Curative vaccination has no sound experimental basis, but the application of the general principles of immunity as well as clinical observation offers a plausible basis for the treatment of localized, more or less chronic infections, and of "carriers." On the other hand, no satisfactory basis is at hand for curative vaccination in the acute self-limited diseases characterized by general dissemination and systemic infection. All attempted vaccinations in this group must be considered as purely experimental. The only logical method of vaccination is the use of "autogenous vaccines." Mixed vaccines, commercially prepared, constitute a type of bacterial polypharmacy which should be discouraged as unscientific and non-ethical. Therapeutic vaccination, if it is to be placed on a scientific basis, should be regarded as a method of treatment based on the study of the individual and his infection and not as a ready-made method capable of the universal application of stock vaccines. The use of vaccines in diseases of doubtful or unknown etiology is unscientific and ethically indefensible. Every physician practicing vaccination should bring to bear in the study of his results every method of laboratory and clinical investigation which promises light, and preferably should work with a trained immunologist. Thus only can definite knowledge of the efficacy of vaccination be obtained. It is well to remember the words of A. E. Wright in this connection. Wright asserts that for such skilled service as that demanded by vaccine therapy "is required a man who has spent years of study to master the technique, to know how to make the vaccines, to know where to look for the microbes, to know which are the most important microbes, to know how to isolate them, and, most of all, a man with sufficient experience and ability to apply all these things." In the interpretation of results it should be borne in mind that, as Theobald Smith has emphasized, vaccines rarely, if ever, cure, but act rather in aiding a process which tends to recovery by stimulating a languid process to immunization.

Splenectomy in Pernicious Anemia.—MOSSE (*Berlin. klin. Woch.*, 1913, l, 2088) describes a case with blood changes similar to those of pernicious anemia in which an apparent cure followed splenectomy. For this treatment to be successful, Mosse believes that the blood should show evidences of hemolysis. This can be determined by testing the resisting power of the red cells to salt solutions of varying strengths and to the patient's serum and alien sera. It is unusual to find evidence of increased fragility of the red cells in true pernicious anemia, as many observations have shown that the red cells in pernicious anemia are more resistant to hemolysing agents than normal red cells.

PEDIATRICS

UNDER THE CHARGE OF

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Malaria in Infants.—WILLIAM WESTON (*Archiv. Pediat.*, 1914, xxxi, 244) points out the influence of malaria on the morbidity and mortality of infants wherever the disease prevails endemically. Of the predisposing etiological factors age comes next to location. In Southern States, malaria reaches its height in July, August, and September. The pernicious types are most often seen in the early autumn. The principal forms of malaria found in the south are the tertian and estivo-autumnal. Pernicious malaria is an intensified degree of infection and not a pathological entity. In the latter condition large numbers of parasites are found in the brain at autopsy, the infantile nervous system being an important predisposing factor. The incubation period in malaria is from three to five days or less. Successive infections of tertian and quartan malaria at different periods may confuse by the attacks occurring daily. The attack usually begins abruptly with vomiting or convulsions, pallor of the skin, followed by cyanosis, followed again by reddening of the face, the nose remaining white and pinched. Temperature and pulse are high. Perspiration accompanies the fall of temperature and prostrations is severe. Infection by the estivo-autumnal type is almost always severe. Enlargement of the spleen and liver are usual, with gastro-intestinal disturbances and often acute pulmonary congestion. A diagnosis can usually be made by examining the blood taken at the beginning of a paroxysm, especially before quinine has been given. The finding of melanin in the large mononuclear leukocytes is said to be pathognomonic of malaria, but more diagnostic of chronic than acute malaria. Other valuable aids in the diagnosis are the therapeutic test, with quinine and the periodicity of the symptoms. Preventive measures, such as destroying the breeding places of mosquitoes, the screening of houses, and keeping children indoors after nightfall are highly important. Quinine bisulphate in aqueous solution is begun three hours after the child's temperature has become normal, giving 2 grains every four hours for twenty-four hours. After this period 3 grains are given morning and evening for three weeks. In pernicious malaria a 3-grain tablet of bimuriate of quinine and urea is given by means of a hypodermic syringe and injected deep in the muscles every six hours. By rectum the bimuriate is given in 6- to 9-grain doses dissolved in salt solution.

Smallpox in Infants and Children.—WILLIAM HANNA (*British Jour. Child. Dis.*, 1914, xl, 1) gives statistics of smallpox epidemics in England to show its incidence and mortality in children, and to demonstrate the fact that the prevalence of the disease has been greatly checked by vaccination. A study of the smallpox records of the Liverpool hospitals for the last ten years shows that among the

well vaccinated no cases are to be found under two years and only seven cases between two and five years of age. The immunity conferred by vaccination in infancy which protects the infant in early life, gradually loses its effect and cases begin to appear in the older children. However, these cases are never as severe as in those who never were vaccinated. No severe cases are to be found. Between two and five years 100 per cent. are very mild cases, between five and ten years 90 per cent. are very mild, and between ten and fifteen years over 80 per cent. are in the same category. Smallpox may occur concurrently with vaccinations. Concurrent vaccination, if done within the first three days of infection, almost entirely neutralizes the smallpox, so that no symptoms or signs of the disease appear or the attack will be very mild, with a few papules which do not mature but simply die away. The later in the incubation stage that vaccination is performed, the more severe the type of disease, but the disease is never more severe than of moderate severity. Vaccination performed after the symptoms have developed does not "take" typically, and the disease pursues its usual severe course. In unvaccinated children, smallpox is always severe, and the records show that up to fifteen years 50 per cent. of the cases are of the confluent type and die, while only 10 per cent. escape with a mild type of eruption. Among the vaccinated the deaths are absoluetly *nil* up to fifteen years. The chief point in the diagnosis of smallpox is the relative distribution of the rash on the different parts of the body.

OBSTETRICS

UNDER THE CHARGE OF

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Cervical Cesarean Section for Double Development of the Genital Organs.—BENTHIN (*Monatsschrift f. Geburtshülfe und Gynäkologie*, 1912, Band xxxv, Heft 2), reports a case of a patient brought to clinic with beginning abortion. On examination, a double vagina was present, terminating on the right side in a retroflexed uterus in which pregnancy was developing. The vagina upon the left side was very narrow, and the cervix on the left side was but partly developed. Thirteen months later the patient again came to clinic in labor, having had uterine contractions for ten hours. The ovum had developed again in the right uterine cavity. Cultures taken from both vaginæ showed the presence of staphylococcus albus. The membranes had ruptured, the fetal head was standing transversely at the pelvic brim. After some delay the head partially descended, when progress ceased. It was impossible to bring the fetus in the axis of the pelvis, and accordingly, cervical section was performed by suprapubic incision. On

examining the tumor, the lower uterine segment of the pregnant uterus was found greatly distended. The delivery of the child proceeded without difficulty, but some delay was experienced in delivering the placenta, which was attached at the fundus. It was interesting to note that uterine contractions occurred in the pregnant uterus only, and not in the left side of the double organ. The mother recovered, but her convalescence was delayed by an attack of bronchitis. In speaking of cervical extirpation in general, Benthin states that he has performed 19 operations, with one maternal death from apoplexy in a uremic patient. He quotes Döderlein's 32 cases, with 3 deaths, and his recent statistics of 50 cases with 3 deaths. KÜSTER has operated 55 times with 2 deaths. Baisch in 16 cases saw lacerations of the perineum during operation. It is Döderlein's opinion that drainage should be employed in the connective tissue of the pelvis after this operation, as it is very difficult to secure primary union in this tissue. The entrance of bacteria into the connective tissue of the pelvis is much more serious than the entrance of bacteria into the abdominal cavity. It is important not to wait too long after rupture of the membranes, because of the danger of infection through the ascent of bacteria from the vagina into the amniotic liquid and amniotic cavity.

Vaginal Cesarean section for eclampsia is reported by BECKMANN (*Monatsschrift f. Geburtshülfe und Gynäkologie*, 1912, Band XXXV, Heft 2), he reports 43 operations, 25 on primiparæ and 18 on multiparæ. In Russian literature, Beckmann has collected in addition to his own, 53 cases. He preceded the operation by the use of the dilating bag, which greatly facilitated the procedure and made it unnecessary to open the posterior cervical wall in all but one case. In all but one patient labor was terminated by version and extraction. Forceps was used once where the head was low in the pelvic cavity. The uterus was tamponed three times to prevent relaxation. The placenta was delivered in 7 cases; in 32 Credé's method was employed, and in 4 the placenta was extracted manually. The paravaginal incision recommended by Dührssen, was necessary in but 4 among 25 primiparæ in whom the children were above the usual size. In one case the uterine wall ruptured because the dilating bag had not been sufficiently filled to procure full dilatation. Dührssen's mortality in vaginal Cesarean section was stated to be 1 per cent. In his 43 cases, Beckmann had 8 deaths, two from septic infection, a septic mortality of 4.6 per cent. By other methods of treatment in the St. Petersburg hospitals, the septic mortality of eclampsia has been 5.7 per cent. Beckmann also compares the results of conservative methods in the treatment of eclampsia prior to 1910 with prompt delivery as performed in 1910 and 1911. In the former there were 210 cases, with a mortality of 32.9 per cent. In the latter two years, 96 cases with 18 per cent. mortality. When the mortality of different methods of delivery in eclampsia is compared, it is found that the forceps had 33 per cent. mortality, spontaneous labor 10 per cent., version and extraction 14 per cent., abdominal Cesarean section, no mortality, and vaginal Cesarean section 18 per cent. It is observed that the more promptly operation is performed the better the results. The fetal mortality is also lessened by prompt operation.

The **Determination of Fetal Age by the Graphic Method.**—Heuser (*Zeitschrift f. Geburtshülfe und Gynäkologie*, 1912, Band lxx, Heft 2), draws attention to Zangemeister's curves in estimating the age of the fetus. Heuser takes as important data the length of the fetal body, height of the occipitofrontal circumference of the head, the occipitofrontal diameter of the head, the depth of the head measured from the chin to the middle of the anterior fontanelle, the circumference of the breast at the nipples, the distance from the umbilicus to the breech or buttocks, the length of the legs and the length of the feet. With each measurement, so near as possible, the duration of gestation is also considered. These are all represented graphically, and their comparison to the normal enables one to judge of the degree of fetal development.

Hannes (*Zeitschrift f. Geburtshülfe und Gynäkologie*, 1912, Band lxxi, Heft 3,) writes concerning the development of the fetus in relation to the duration of pregnancy. He draws attention to the fact that the fetus at full term may vary greatly in weight and development. He finds that when the fetus is above the average in weight that considerable variation in length may be present. The average, however, in these healthy children will be from 53 to 56 cm. In cases where there was no information concerning the last menstruation, it was found that the weight of the fetus served as a constant indication of the period of gestation. In but 50 per cent. of large children was pregnancy prolonged 280 days.

The determination of fetal sex in utero is the subject of a paper by Petri (*Zeitschrift f. Geburtshülfe und Gynäkologie*, 1912, Band lxxii, Heft 1). His method consists in the use of serum obtained from the cow and the steer, and in 7 cases where injections were made and the serum dilated from one-half to one in forty, the results indicated the sex of the child. As control, the Wassermann test was found in some cases negative, and in others positive. While the experiments gave results of interest, they were not conclusive, and could not be relied upon to positively determine the sex of the unborn fetus.

Obata (*Zeitschrift f. Geburtshülfe und Gynäkologie*, 1912, Band lxxii, Heft 3), contributes an interesting paper upon the centres of ossification in the fetal pelvis. He finds that the centres of ossification in the ischium, pubis, ilium, first to fifth ribs, and portions of the spine, develop bilaterally during fetal life. There is unilateral development in the sacrum. All these centres of ossification seem to be composed of one mass and not of several parts. These various centres differ in length and in shape. The deposit of calcium in the ossification centres is characterized by the growth of bone cells and the gradual disappearance of the ossification centre itself. The so-called chondral reaction is found in the fetus 30 mm. long, first in the ilium, although in other bones it may be wanting. In the ilium the chondral reactions begins a short time before the deposit of calcareous material. Among many misstatements frequently made concerning obstetrics cases, that of excessive fetal size is probably the most often in evidence.

Ahlfeld (*Zeitschrift f. Geburtshülfe und Gynäkologie*, 1912, Band lxxii, Heft 3), has collected previously reported cases of excessive fetal size. At the head of the list stands Ortega's case, 11,300 grams, 70 cm. long; the sex a male. Rachel and Neumer report a child 11,250

grams in weight. Beach, one of 10,750 grams in weight, in length 76 cm.; the sex a male. Olano, a female child 68 cm. long and 10,000 grams in weight. Thence the weight gradually descends to that of Baudeloque, who reports a female child 61 cm. long, weighing 6150 grams. The question naturally arises, Under what circumstances does this excessive development of the child occur? First in importance is the development of the parents. If they are excessively large and stalwart, the offspring shares in their size. There is also a tendency where the mother is well nourished to an increase in fetal size, with an increasing number of pregnancies. It is well recognized that when pregnancy occurs comparatively late in life that the tendency to overgrowth of the fetus is also present. Unquestionably the growth of the placenta and its area has something to do with this condition. The percentage of male to female children is two to one. Prolongation of pregnancy is also a cause for excessive fetal growth, which has long since been recognized. Labor is delayed in these cases because the excessive size of the head prevents its normal descent into the pelvic brim and retards labor through the absence of the pressure of the head upon the lower uterine segment and cervix. The mortality among large children is very great. In 62 cases, 50 were dead-born, three were moribund, and but nine were delivered in good condition.

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GYNECOLOGY

UNDER THE CHARGE OF

JOHN G. CLARK, M.D.,

PROFESSOR OF GYNECOLOGY IN THE UNIVERSITY OF PENNSYLVANIA, PHILADELPHIA.

Endometritis and Uterine Hemorrhage.—Although the trend of modern opinion is for the most part away from the old idea that endometritis is of itself ever the real cause of excessive uterine hemorrhage, DRIESSEN (*Zentralbl. f. Gyn.*, 1914, xxxviii, 618) believes that there is one very definite type of endometritis which does stand in this relation to metrorrhagia. He also, in contradistinction to some modern authors, maintains the correctness of the older view that at each menstrual period actual bits of the surface mucosa are cast off and discharged from the uterus; this he has proved by carefully collecting and examining the menstrual blood. He believes that this occurs in the following way: In the premenstrual stage the endometrium becomes differentiated into two layers, a compact and a spongy. The former, and part of the latter, undergo necrosis, accompanied by an invasion of polymorphonuclear leukocytes. Numerous small bloodvessel ruptures, with consequent hemorrhages, occur; these hemorrhagic areas then

become organized by the ingrowth of young fibroblasts. The necrotic portions are cast off, and the newly formed stroma is covered with a new epithelium, whose cells show active proliferation. This is the normal process, and is associated with normal ovarian activity. In some cases of irregular menstruation, however, associated with an insufficiency of ovarian function—a condition that is especially apt to occur about the time of puberty or the menopause—the necrotic portions of the old endometrium are not cast off, but remain attached to the surface, just as bits of placental tissue remain after an incomplete abortion. As a result of this, Driessen thinks, a peculiar type of endometritis arises, which may be the cause of profuse hemorrhages. Pathologically, this type of endometritis is characterized by the occurrence here and there in the stroma of *hyaline masses*, the result of non-organized hemorrhages; these are always surrounded by masses of leukocytes. The glands may show some cystic dilatation, and the epithelium may be multilayered, almost suggesting malignancy. It is evident, Dreissen thinks, that the presence of these hyaline and necrotic masses, acting as foreign bodies, causes the active inflammatory infiltration of the endometrium, and that the incomplete regeneration of the stroma causes compression of the gland outlets and dilatation of the deeper portions. Just as bleeding after an abortion does not cease until the placental remains are removed from the endometrium, so the menstrual bleeding associated with this type of endometritis persists until either the incompletely cast off necrotic areas are removed by curettage, or the ovarian function is completely destroyed by oöphorectomy or the *x*-ray. For the majority of these patients, Driessen considers the last named method of treatment the most satisfactory.

Amniotic Membrane for the Prevention of Postoperative Adhesions.—Undoubtedly one of the most difficult problems encountered by the abdominal and pelvic surgeon is the prevention of adhesions between peritoneal surfaces from reforming after their separation, or from occurring after operations in infected areas. Many forms of artificial and animal membranes, oils, etc., have been tried, with practically no result. An interesting suggesting is now made by LYMAN and BERGTOLD (*Surg., Gyn., and Obst.*, 1914, xviii, 762) to use human amniotic membrane for this purpose. It appears to have several distinct advantages, in that it is easy to obtain in sheets of large size, it is originally sterile, can be easily preserved and kept sterile, and is thin, easy to handle, and is probably easily absorbed. Lyman and Bergtold report its use in seven cases, with very gratifying results; one of the patients was a young woman who had been operated upon twice for the relief of adhesions throughout the abdomen, without benefit. A third operation was performed, with free use of the membrane, and was followed by complete relief of the symptoms, a condition which has lasted for over five months since operation. The amniotic membrane is obtained from a patient free from constitutional disease; it is prepared by washing in running water for two hours, and is then preserved until wanted in a 0.5 per cent. solution of formaldehyde in 70 per cent. alcohol.

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Disposal of Unaffected Tube in Operation for Ectopic Pregnancy.—In order to formulate if possible some rational scheme of dealing with this often very puzzling question, R. R. SMITH (*Surg., Gyn., and Obst.*, 1914, xviii, 684) has collected from various American surgeons the records of 192 cases, all of which have been followed for at least five years after the original operation. In 48 of these patients, the operation was of such a character as to preclude the possibility of further pregnancy, and these are therefore not taken into consideration. Of the remaining 144, in whom the subsequent occurrence of pregnancy was at least theoretically possible, 47 (or almost one-third) actually became normally pregnant, some of them several times, resulting in the birth of 64 children. In 21 women a second ectopic gestation occurred, in the tube which had been left at the original operation. In 2 instances, living children were born, and subsequently a second ectopic occurred. As a result of the facts brought out in this investigation, Smith says that he has adopted the general principle of preserving the childbearing function in the younger women wherever it is at all possible to do so, even at the risk of a subsequent tubal pregnancy, but in older women, with whom the need of children is no longer so urgent, he thinks the best interest of the patient is usually served by preventing the possibility of a second ectopic gestation. He thinks that in each individual case the whole matter should be freely discussed with the patient, when this is possible, and a certain amount of weight be given to her wishes. In short, the age of the patient, the number of children she has borne, her general health, and her wishes as to further pregnancies should all be taken into consideration, and these factors should play a much more important role in forming our judgment than the gross appearance of the unaffected tube at time of operation, from which, as a rule, nothing can be told as to its future functional capacity.

Causes and Treatment of Chronic Backache.—There is probably no single symptom that appears on the records of so large a proportion of gynecological, or supposedly gynecological patients, as does *backache*. While it is undoubtedly true that in many instances the cause of this condition lies wholly within the genital organs, it is equally true that in a perhaps larger number it lies either partly or wholly outside of the sphere of gynecology in its narrowest sense. The fact, however, that in so many cases the trouble is partly due to malpositions, inflammations, etc., of the pelvic organs, and partly to other conditions altogether, should serve to emphasize that here gynecology and orthopedics approach so close as to be practically inseparable, and that the broad-minded gynecologist cannot afford to neglect wholly the orthopedic side of the question, if he would avoid the performance of many needless, if not harmful, manipulations or operations within the female pelvis. In this connection, a recent article by an orthopedist, LOVETT (*Jour. Amer. Med. Assoc.*, 1914, lxii, 1615) is of considerable interest. After eliminating tuberculosis of the spine, organic nervous disease, and the results of spinal fracture, he says that in investigating the causes of chronic backache, three etiologic classes can be identified, about which there is no reasonable doubt: (1) Disease or displacement of the pelvic organs. (2)

Traumatism to the back. (3) Arthritis of the spine. Having defined and set aside the cases belonging to these divisions, however, there still remains a large group, with regard to which there are two chief points of view, (1) that they are largely *static* in origin, due to overstrain of the posterior musculature, and (2) that they are due to a strain or relaxation of the *sacro-iliac joints*. The latter explanation, Lovett rejects for all but a very few exceptional cases. He does not consider that any *x*-ray or pathological evidence has ever been adduced to warrant us in believing that any considerable relaxation of these joints, sufficient to produce symptoms, actually occurs. Moreover, he does not think it possible that any of the forms of treatment commonly advocated for this supposed condition, such as elastic silk trunks, strips of adhesive plaster on the skin, a webbing belt, plaster-of-Paris jacket, etc., could possibly jam these joints firmly enough together to prevent their slipping by each other, were they inclined to do so, and the fact that in many instances these measures do give very positive relief is, in his opinion, good evidence against the correctness of the diagnosis. The majority of cases of this type Lovett believes to be in reality static in origin, due to defective lateral balance or to defective anteroposterior balance. If for any reason, one leg is longer than the other, the pelvis will become oblique, and the muscles of one side will be put under more strain than those of the other, and thus backache due to defective lateral balance arises. arises. In cases where the abdomen is so large as to cause a serious anterior load, the anteroposterior balance may be disturbed, as well as by flat-foot, a relaxed and slumped attitude, etc. In most of these cases, relief will be afforded by correct shoes and corsets. In many of the mixed cases, *i. e.*, where the pelvic organs and static conditions appear to play a role, Lovett advises trying mechanical treatment for a time, before resorting to operation, while in other instances, in which gynecological attention is clearly indicated primarily, treatment of the static element may be subsequently necessary to produce a complete cure.

HYGIENE AND PUBLIC HEALTH

UNDER THE CHARGE OF

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School Diseases.—Edwin O. Jordan (*Jour. Amer. Med. Assoc.*, 1913, lx, 409) says there is much to favor the opinion that school attendance plays a large part, if not the chief part, in the dissemination of infectious diseases among groups of children of susceptible ages. The

school furnishes specific opportunities for infection in the friendly exchange of pocket-handkerchiefs, lead-pencils, and chewing gum. The discharge of minute droplets of spray from the mouth or nose during sneezing or coughing is also a danger difficult to guard against. The school playground as well as the school-room must be considered as having a bearing on school diseases. A wide divergence of opinion exists as to the actual proportion of cases contracted through the agency of the school. Conditions are not alike in all infectious diseases, particularly in measles, scarlet fever, and diphtheria. Investigations by Kingsford in Liverpool and Roger in America tend to emphasize the importance of school attendance in spreading measles. Scarlet fever seems to be less generally considered a school disease. Many investigations point to the milk supply as a prominent factor in spreading the disease, and there is a growing disbelief in the importance of school infection. In the case of diphtheria, while there is a difference of opinion, still there are numbers of outbreaks of the disease reported in which the connection with school attendance could not be doubted. In this disease the "diphtheria carrier" plays the important role in school infection, and when school attendance is regulated by bacteriologic findings, school epidemics quickly subside.

Reinspiration of Expired Air.—Crowder, (*Archiv. Int. Med.*, October, 1913, xii, 420–451) has made a study of the reinspiration of expired air. By this phenomenon is meant the immediate reinspiration of a portion of our expired breath. This occurs quite commonly, in fact, may almost be regarded as a normal accompaniment of respiration during the major part of our lives. Lehman ("Der Kohlensäuregehalt der Inspirationsluft im Freien und im Zimmer," *Arch. f. Hyg.*, 1899, xxxiv, 315) and also Heymann ("Ueber den Einfluss wieder eingeathmeter Expirationsluft auf die Kohlensäure-Abgabe," *Zeitsch. f. Hyg.*, 1905, xlix, 388) determined the CO_2 of the inspired air, compared this with the CO_2 of the surrounding air, and from the difference computed the proportion of the breath which was reinspired. They found this proportion to vary greatly. It was sometimes more than 6 per cent., but dropped to zero in the open air, and in a breeze of 3 meters per second. Crowder confirms these observations and extends them much further. He shows that under many conditions the air about the face contains much more CO_2 than the surrounding air. The path of the expired air may roughly be seen by watching the course of smoke blown from the nostrils. The expired air leaves in a cone-shaped expansion, part of which lies quite close to the body, and then rises slowly by convection currents. Inspiration follows expiration immediately, therefore every chance is offered for some of the expired air to be again drawn in, except when facing a breeze of from 200 to 300 feet per minute, or when walking, riding, or fanning. When the back is turned to a breeze a little of the expired air is often reinhaled in spite of the current. The position of the head influences the amount of air rebreathed. Thus Crowder has shown that while sitting upright the reinspiration was 2.3 per cent.; lying down with a pillow tilting the head forward, 1.3 per cent.; lying flat, head thrown back, none at all. In the ordinary position in bed, with the head on the side and flexed, with pockets or dead spaces for the air to stagnate, there will

be a greater retention of expired air. This occurs especially when the head sinks into a soft pillow. It may be concluded that when one lives indoors and remains quiet he will immediately rebreathe from 1 to 2 per cent. of his own expired air; in bed it will be more, from 1 to 5 per cent., and even 10 to 18 per cent., depending on the position in which he lies. Nor does sleeping in the open insure pure air for breathing, especially when one buries his head between pillows and bedclothes for the sake of warmth. The significance of respiration and its mechanism with reference to the phenomenon of reinspiration of expired air is reviewed in a masterly way. The factor of safety indicates that slight amounts of CO_2 in excess may be compensated for and probably are not deleterious. It is again shown that a good system of ventilation requires cool, moving air with a proper humidity in order to maintain the thermic balance of the body and to stimulate its chemical activity. "A little extension of the dead space beyond the tip of the nose is of no consequence."

PATHOLOGY AND BACTERIOLOGY

UNDER THE CHARGE OF

JOHN McCRAE, M.D., M.R.C.P.,

LECTURER ON PATHOLOGY AND CLINICAL MEDICINE, MC GILL UNIVERSITY, MONTREAL; SOME TIME PROFESSOR OF PATHOLOGY IN THE UNIVERSITY OF VERMONT, BURLINGTON, VERMONT; SENIOR ASSISTANT PHYSICIAN, ROYAL VICTORIA HOSPITAL, MONTREAL.

Tissue Metaplasia in Grafts.—SMITH (*Jour. med. Research., August*, 1913, xxviii, No. 3) reports the results of interchanging epithelial linings from one organ to another. Thus he grafts the gall-bladder lining upon the urinary bladder, and *vice versa*, as well as utilizing the uterine covering in both organs. The epithelium of the gall-bladder and uterus became replaced in the urinary bladder by a transitional epithelium, and the epithelium of the urinary bladder and uterus was replaced by the columnar epithelium of the gall-bladder when transplantation was made into that organ. This is doubtless due to the fact that the regional epithelium is in a better position for proliferation than the graft epithelium, and Smith does not attempt to suggest that an actual transformation from one type of cell to another occurs. When the epithelial tissue of two types is transplanted side by side into the peritoneal cavity, a cyst is formed in which both tissues independently take part, and in which neither one displaces the other. When invasion and replacement of one epithelial tissue by another takes place, as in the foregoing experiment, Smith thinks that the environmental conditions act unfavorably upon the one, and favorably upon the other. This is exactly what might have been expected; nevertheless we mention the subject because of the ingenious methods which are used to provide the proof.

The Mechanism of Lead-poisoning.—Erlenmyer (*Zeitsch. f. Exper. Path. u. Therapie*, September 16, 1913, Band xiv, Heft 2) has undertaken experimental studies for the purpose of determining whether chronic lead poisoning depends upon an accumulated mass of the metal in the body, or upon the existence of a more or less concentrated solution of lead in the circulatory cell fluids, and cell fluids in general; that is, upon the existence of what Erlenmyer calls a "lead-stream." He declares in favor of the latter, and his contention can scarcely be better explained than by giving the example of a woman who worked with cyanide of mercury and lead during an eight-and-a-half-hour day for long periods in perfect health. When her day's labor was lengthened to ten and a half hours, in three months she developed severe symptoms of chronic lead poisoning from which she recovered in the next three months. She again resumed her work at eight and a half hours per day, and during the next year remained perfectly well. The explanation was that in eight and a half hours per day she never attained the concentration of "lead-stream" which meant the minimal toxic dose, but that in ten and a half hours daily work she did. Erlenmyer has performed a large series of very painstaking experiments, and considers that the relatively insoluble lead salt enters into a solution-like relationship with the body substances, so that a lead albuminate combination is thrown into the circulation, flows through the blood, and is in part excreted through the urine and feces. Lead in such combination comes into relationship with all the cells of the organism in its way through the body, but does not tend to be retained in a constantly increasing amount. It is true that if certain organs be examined for lead, it is found, in the nervous system, for example, and in the blood and other body juices. Yet this does not mean that the metal actually enters into the cells and becomes anchored there as an alkaloid might. Nor is it likely that the lead which was dissolved, and was carried in a soluble form in the circulation, became precipitated in the individual cells, or formed a permanent chemical combination with the cell molecules. Riva has shown that in animals which had been injected with lead acetate, the lead was only found in combination with the globulins, while the nucleoproteins remained free; which seems to show that lead is actually present in solution as lead albuminate, and remains in this soluble form throughout. The element of time must also be considered in the accomplishment of a chronic poisoning by lead. Erlenmyer states that we can form a kind of ratio between the body weights and the amount of lead, and the time which elapses. He found that 1 mg. per 1000 gm. body weight produced a fatal result in fifty to sixty days, and that the minimal amount was 0.7 to 1 mg., although in certain animals more than one might be required. But the density and concentration of the "lead-stream" is more important than the duration of time. This formula was determined in cats which were injected subcutaneously with lead carbonate, and in such animals the definite, permanent retention of lead does not occur.

Tobacco and the Blood-pressure.—John (*Zeitsch. f. Exper. Path. u. Therapie*, September 16, 1913, Band xiv, Heft 2) has conducted a most painstaking series of observations on the effect of smoking upon

the blood pressure. He finds that the smoking of two moderately strong cigars is sufficient to produce entirely characteristic variations of blood pressure. During the time of smoking there is a definite increase of the diastolic pressure, and a primary increase of systolic pressure, with a subsequent fall. These alterations are observable for as long as two hours after smoking has ceased. John considers that the result is brought about by the stimulation to contraction produced on the vessel walls, whereby heightened tonus is produced, a fact which has been experimentally determined. Pulse frequency is not always affected in the same way, sometimes the pulse is actually slowed, but usually there are greater variations than are to be observed in a control. Eight to ten Russian cigarettes produced the same result upon the blood system as two moderately strong cigars, and between various kinds of cigarettes very different observations were made. The observer found that even four cigars of a certain brand which he names, did not influence the blood pressure in the slightest, due probably to the fact that they are very poor in nicotine. Eight to ten cigars divided over a day are not entirely without effect upon the blood pressure; but there are so many influences that affect the blood pressure in the course of the daily life, that it is a little difficult to lay the blame definitely upon the tobacco. Cigars poor in nicotine, however, produce decidedly less effect than those which are strong in nicotine; while twenty-five or thirty cigarettes produce an effect scarcely to be distinguished from that of eight to ten moderately strong cigars. John considers that the result of his observations is that a definite influence upon the bloodvessels has been once more proved, and that nicotine is able to produce vascular changes of an arteriosclerotic nature. John goes on further to state that coronary disease should be the signal for an uncompromising attitude against the use of tobacco, and disposes of the argument that many old men with coronary disease smoke enormously without killing themselves, by stating that this does not speak for the harmlessness of tobacco, but for the enormous resistance which certain individuals possess.

Tuberculin in Healthy Animals.—KLOPSTOCK (*Zeitsch. f. Exper. Path. u. Ther.*, April, 1913, Band xiii, Heft 1) finds that repeated subcutaneous injections of old tuberculin begun at 0.1 to 5 c.c., and totalling as high as 26 c.c. for a single animal, the doses administered at intervals varying between three days and a month, gave no reaction in the majority of test animals. Six guinea-pigs out of 20 died of peritonitis. Animals so treated with tuberculin showed no increased resistance to subsequent infection by experimental means, nor did the course of the disease or the appearance of the organs at autopsy indicate any differences from control animals. The sensibility of animals first injected with tuberculin and subsequently injected by tuberculosis was found to be diminished. Repeated doses of tuberculin produced no formation of antibodies in healthy guinea-pigs.

Spirochetes.—ARNHEIM supplements his previous observations upon spirochetes, made at the Robert Koch Institute in Berlin (*Zeits. f. Hyg. u. Infekt.*, 1914, Band lxxvi, Heft 3). He used spirochetes from syphilitic material and some strains of refringens. It needs but a short period

of cultivation to develop involution forms, as well as degenerated individuals, and in cultivation the virulence falls very rapidly, so that inoculation of animals from cultivated organisms is very much the exception rather than the rule. Arnheim's experience leads him to realize that the sharp distinction once drawn between pallida and refringens are inaccurate; for in material from animals infected with pallida he finds forms so closely resembling refringens that differentiation is difficult. Insofar as agglutination and precipitation of pallida by specific sera, he found no affirmative evidence at all. Complement fixation by cultivated spirochetes in the serum of syphilitics occurs, of course, but he thinks in a lesser degree of intensity than the Wassermann reaction, and the reactions restrained by non-specific agents are rather numerous. The complement fixation reaction is not quite so dependable as the Wassermann, and both failed occasionally for unknown reasons. When cultivated spirochetes are kept in continuous contact with their poisons, Arnheim did not find that isolated individuals escaped, subsequently to multiply. Arnheim experimented also with swine pest and concludes that it is not caused by spirochetes, but that the spirochetes there discovered are saprophytic.

Lipoid Infiltration.—Jastrowitz (*Zeits. f. Exper. Path. u. Ther.*, January, 1914, Band xv, Heft 1) publishes from Halle a very painstaking study upon the foregoing subject. The points of interest do not lie so much in the question of the amount of infiltration as the processes of synthesis by which the fat content of organs is made up from simple lipoid substances. It does not simplify the problems that in certain forms of poisoning there occurs a transportation in the blood of fat from the body depots to the great body organs: in fact, this may be so great in amount that it overshadows and hides in severe poisonings the variation in the lipoids of the organs concerned. On the other hand, however, in certain forms of poisoning, such as by arsenious acid and nitrobenzol, the fatty infiltration is slight, and the lipoids can be observed to be much increased in the blood, and in such an organ as the kidney. The phosphatids may at times in an organ be absolutely and relatively decreased, and under yet other circumstances actually increased by reason of the transport of fat by the blood; but at the same time the phosphatids relative to the total lipoids are decreased. In cases of marked fatty infiltration, the amount of lipoids is likely to be great, corresponding to the well-marked anatomical visible change; in infiltration that anatomically appears slight, it does not follow that the lipoid content is correspondingly low.

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